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GUANIDINE AND THE PARATHYROIDS

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Even a cursory examination of microscopic sections from the parathyroids removed at the routine autopsies is sufficient to make one realize how scanty is the basis upon which any histological interpretation may be made.

In even a small collection of sections from the parathyroids, the variety of appearances which are usually seen, suggests that factors either normal or pathological have the power to change very appreciably the state of the circulation in the glands, the amount of globulation in the epithelial cells, and the proportion of the eosinophile cells present.

These are the problems to be considered.

In order to establish the necessary histological basis for further interpretation, it is necessary to correlate the functional states of the parathyroids with some definite histological appearances. As a result of the work of Paton and Findlay, and their co-workers, it is known that varying degrees of hyperactivity can be induced by the injection of

guanidine. Our initial task, therefore, is to find some distinct histological features indicating hyperactivity of the glands.

Since the following experiments are based on the findings of Paton and Findlay, it is necessary to keep in mind their conclusions. They are of the opinion that the parathyroids control the metabolism of guanidine in the body, by preventing its development in excessive amounts. Since, according to these authors, guanidine is responsible for the maintenance of muscle tone, the glands exercise a regulative action over them.

Schafer considers that the parathyroids produce an autocoid which is passed into the blood stream. This autocoid promotes protein metabolism and enables intermediate products such as guanidine to be further metabolised. Collip has partially isolated this active principle.

The conclusions of these workers suggest that, by the introduction of a guanidine compound into the animal, its parathyroids must become more active to counteract the effects of the guanidine compound. If this hypothesis be correct, a series of injections at various intervals would give a microscopic picture of the gland at rest, in various stages of activity, or perhaps, even, in a state of functional strain.

HISTOLOGY

The histology of the parathyroids has been described in detail by Sandstroem, Kohn, Welsh, Benjamins, Erdheim and Thompson. Briefly, their findings are that the cells are divided into two types.

There are the comparatively small cells with large, deeply staining nuclei, colorless cytoplasm and a distinct cell border. These cells constitute by far the greater part of the glands.

In the other division are the large eosinophilic cells with small nuclei, granular cytoplasm, and a distinct cell outline. These cells are seldom numerous in normal glands, and in some sections they may be absent.

It is often possible to find cells with features of both types. This would seem to suggest that the variations only signify different phases of functional activity in a single type of cell,—which is the view held by Schafer.

Another important feature is that the cells and the connective tissue of the parathyroids may contain a considerable amount of fat (Thompson, Benjamins and Welsh). The intracellular fat in the parathyroids of the rabbit takes the form of numerous and conspicuous large globules.

EXPERIMENTAL DATA

Only the microscopic features of the parathyroids are being discussed here, as the other aspects of the effects produced by guanidine injections are dealt with fully by Paton and Findlay, and their co-workers.

Adult rabbits were injected, chiefly intravenously, with a 5% solution of guanidine nitrate in normal saline. The tissues were fixed in Helley's fluid. The sections were stained with hemalum and eosin, and with acid fuchsin and methyl green.

In order to investigate the nature of the globules present in the parathyroids, half of each glandule, from a number of animals, was fixed according to Regand's method and the sections were stained with acid fuchsin and methyl green. By so doing, lipoid substances within the gland, to a large extent, were retained and demonstrated.

The following represents a summary of the experiments together with the macroscopic and the microscopic appearances of the parathyroids:

R. 15. 850 gms. aet 4 months.

0.4 gms. per kilogm. of body weight were injected subcutaneously. The animal died in 18 hours.

Macroscopic Examination.

Parathyroids: Intensely congested; one looked haemorrhagic. (Congestion was not so marked a feature of the other organs.)

Microscopic Examination.

Parathyroids: The glandules are intensely congested. The usual large globules are rare (Fig. 1) but small ones are present in appreciable numbers. The cells are pale, indefinite and swollen. Nuclear chromatin is not so abundant as usual. Occasionally there are nuclei showing a distinct achromatosis. A number of the smaller cells possess very dark nuclei.

R. 16. 830 gms. aet 4 months.

0.2 gms. per kilogm. of body weight were injected subcutaneously. The animal died in 20 hours.

Macroscopic Examination.

Parathyroids: No abnormality is obvious to the naked eye.

Microscopic Examination.

Parathyroids: These are congested. Although there are very few large globules, those of the smaller size are quite numerous.

R. 13. 1590 gms. aet 6 months.

Injected intravenously with 0.1 gm. per kilogm. of body weight. Killed in 24 hours.

No abnormality is obvious to the naked eye.

Microscopic Examination.

Parathyroids: There is no obvious congestion. The scarcity of large globules is a conspicuous feature. With the oil immersion lens (1/12) numerous small globules are visible. In general, the cells are large, swollen, granular, and contain numerous small globules.

N. 314.

Injection of 0.5 gms. per kilogm. of body weight. Killed in 48 hours.

There are no obvious macroscopic abnormalities.

Microscopic Examination.

Parathyroids: The large colorless cytoplasmic globules are abundant (Fig. 2). Very few of the smaller and more opaque globules are to be seen.

R. 17. 800 gms. aet 4 months.

Injected intravenously with

0.1 gms. on 1st day. } Per kilogm. of
0.17 gms on 4th day. } body weight.

Killed on 5th day.

Microscopic Examination.

Parathyroids: The cells are massed together and contain very deeply staining nuclei. The cytoplasm is almost uniformly finely globulated. There is a conspicuous scarcity of the large globules. Congestion is only slight.

R. 12. 1440 gms. Adult.

Intravenous injection of 0.1 gms. per kilogm. of body weight. Killed on the 8th day.

On post-mortem examination the parathyroids seemed large and were pale.

Microscopic Examination.

Parathyroids: The cells have deeply staining nuclei and are extremely vacuolated. In the majority these vacuoles occupy the greater part of the extra-nuclear cell structure. Smaller globules are of frequent occurrence.

In sections stained with hemalum and eosin, the cytoplasm of many cells contains opaque granular dark staining masses. Sections stained with acid fuchsin and methyl green show acidophilic granules in the epithelial cells, especially in those which border on capillaries.

There is no congestion.

R. 18. 730 gms. Adult.

Received intravenous injections of

0.05 gms. on 1st day } Per kilogm. of
0.1 gms. on 6th day } body weight.

Killed on the 9th day.

Microscopic Examination.

Parathyroids: While the large globules are not so abundant as usual, the cytoplasm of the cells contains many of the smaller type. The nuclei have stained deeply. The cell boundary is distinct.

R. 14. 1370 gms. aet 6 months.

Intravenous injections of

0.06 gms. on 1st day	Per kilogm. of body weight.
0.08 gms. on 4th day	
0.1 gms. on 11th day	
0.1 gms. on 14th day	
0.12 gms. on 18th day	
0.13 gms. on 20th day	
0.15 gms. on 25th day	
0.19 gms. on 27th day	

Throughout the latter part of this experiment muscular spasm was elicited by the slightest stimulus. The animal was killed 2 hours after the last injection while in tetany.

Post-Mortem Appearances.

Parathyroids: Pale and enlarged.

Microscopic Examination.

Parathyroids: The granularity of the cells is very marked, while the amount of globulation is only moderate. The cells are large and indefinite, while the nuclei are granular, and stain less deeply than usual (Fig. 3). In many cases, there is distinct evidence of hyperplasia. On the whole, congestion is fairly pronounced.

(N. B.—In all except R. 14, eosinophilic cells are rarely seen, while in R.14 they are present in appreciable numbers.)

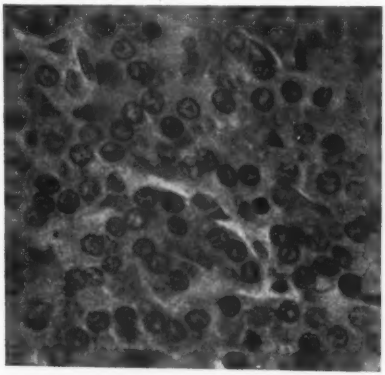

Fig. 1. R. 15; x 550. Hemalum and Eosin. The almost complete disappearance of globules from the gland 18 hours after the injection of guanidine nitrate.

DISCUSSION

What information have these experiments produced?

To answer this, we must consider the relationship of the cytoplasmic globules with parathyroid activity and with guanidine. The appearance and disappearance of these globules after guanidine injections, and the altered appearance of the parathyroid cells, indicate that some relationship does exist.

GUANIDINE AND THE PARATHYROIDS

A section of the normal glandule of a rabbit exhibits a most extensive globulation of the cytoplasm, the globules occupying the greater part of the cytoplasm. These are of a fatty nature. (Thompson, Benjamins and Welsh.)

After the injection of guanidine nitrate, these large globules disappeared in 18 hours (Fig. 1). In their stead, were the very minute globules which at first were recognized only by an examination with the oil immersion lens (1/12).

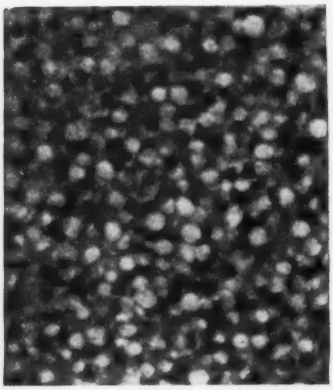

Fig. 2. N. 314: x 500. Hemalum and Eosin. In 48 hours globulation has returned to the normal amount, as seen in the parathyroids of the normal rabbits.

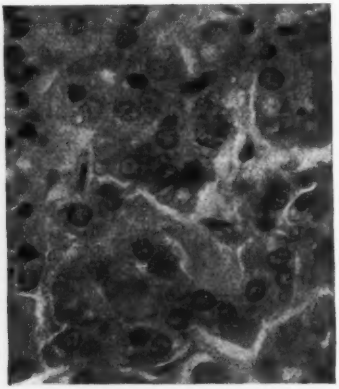

Fig. 3. R. 14: x 650. Hemalum and Eosin. The cells are large, the cytoplasm finely globulated, and nuclei not as deeply staining as usual.

Up to 48 hours, the picture was similar. At 48 hours, the gland had recovered its normal globulated appearance. The small globules had diminished in number. Eight days after a single injection, the glands had an appearance similar to that seen in 48 hours (Fig. 2).

It therefore would seem probable that the variations in size and number of globules within the cells of the parathyroids might give some indication of the functional state of the gland.

Does this correspond with the views held by Paton, Findlay and Schafer? According to these authorities, guanidine should throw the parathyroids into greater activity, in order

that the excess of this substance may be further metabolised.

In R. 15, R. 16, and R. 13, the most striking change in the parathyroids was the disappearance of the larger globules. After 48 hours, the normal appearance returned, as seen in N. 314. The disappearance and reappearance of their large globules had a consistent relationship with the guanidine injections.

In short, up to 24 hours after an injection of guanidine, globules were relatively scarce in the parathyroids. At about 48 hours after an injection, the normal appearance had returned.

But what is the effect of repeated injections? The effect of the second dose was as marked as the first. R. 17 was killed 24 hours after the last injection. The appearance corresponds closely with that of R. 13. However, the later stages of recovery as seen in R. 18 were not so complete as when only one injection was given.

R. 18 was killed in 9 days—3 days after the last injection. The large globules were not at all rare, but in numbers they could not be compared with the picture seen in either N. 314 or R. 12. In R. 18, the small globules predominated. After 3 days, then, the glands had not recovered their normal appearance. There was still a suggestion of hyperactivity.

R. 14 received eight injections in 27 days. The seventh was given on the 25th day and the eighth on the 27th day. The animal was killed two hours after the last injection while in tetany. Latterly the animal was kept in a constant state of muscular hypertonicity. The resultant microscopic picture again showed the predominance of the small globules.

The chief point to be considered in R. 18 and R. 14 is the relationship the smaller globules bear with the activity of the cell. In R. 14, there was a pronounced hypertrophy of the parathyroid cells, and there were many indications of hyperplasia although no obvious mitosis was demonstrable. (Fig. 3.) It therefore seems to be highly probable that the small globules go hand in hand with an increased activity of the glandules. In other words, the cells had not sufficient time to accumulate their product in large enough quantities for the formation of the larger globules. In their place the smaller globules appeared.

It is also significant that only in R. 14 were the granular eosinophilic cells present in any appreciable numbers. MacCallum suggests that an increased eosinophilic granularity of the cells may be associated with increased activity.

Transitional forms were seen between this and the more prevalent type of cell.

It can therefore be concluded that the microscopic evidence supports the views of Paton, Findlay and Schafer on the relationship which exists between the parathyroids and guanidine.

SUMMARY

1. An injection of guanidine nitrate causes the depletion of the parathyroid globules within 18 hours.

2. The normal appearance is restored in 48 hours.

3. Repeated injections, sufficient to keep a constant degree of hypertonicity in the muscles, causes hypertrophy and hyperplasia of the parathyroid cells, as well as a marked increase in the acidophilic cells, and a marked absence of the large globules.

4. Guanidine injections, therefore, involve increased function of the parathyroids as shown by the absence of large globules, the presence of small globules, hypertrophied cells and numerous eosinophilic cells.

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STUDIES IN ACROMEGALY
II. HISTORICAL NOTE*

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Owing to the protean nature of the disease acromegaly, the literature concerning it has grown extremely voluminous. Each one who had an opportunity to investigate the clinical picture or post-mortem findings in a personally observed case was apt to stress the outstanding features presented by his particular patient, with a resulting confusion of opinions regarding the nature and origin of this strange malady. There have thus grown up "schools" of opinion, each championed by some outstanding contributor whose numerous followers have all inserted their personal modifications to the original hypotheses.

It is not the aim of this present note to review the entire literature on the subject of acromegaly, but merely to touch upon those points which appear to be essential to our present conception of the disease. The paper therefore will serve merely as an introduction to certain studies concerning diabetes, metabolism, the rôle of other endocrine organs than the hypophysis, etc., which are to follow.

In 1886 appeared Marie's clinical description (14) of a new disease, based on two cases, to which he gave the name of "acromegaly." He laid the foundation for all subsequent clinical studies by his classical description of these patients, but he made no attempt at the time to ascribe the malady to any particular etiological factor. In addition to these two personally observed patients, Marie also called attention to five other examples obviously of the same condition which had appeared in the literature under a variety of designations. These had been reported by Sauscerotte-Noël (1772), Alibert (1822), and Friedreich (1868), who reported the cases of the famous "brothers Hagner," whom Marie later considered to be examples of osteo-

*For the first of this series of reports, *cf.* Bailey, P., and Davidoff, L. M.: "Concerning the microscopic structure of the hypophysis cerebri in acromegaly." *Am. J. Path.*, 1925, *1*, 185-207.

arthropathy, and by Henrot (1877). On Henrot's patient an autopsy had been done and a large pituitary tumor found.

The next year (1887) Minkowski (19) reported a case of his own which he recognized as similar to Marie's two patients. This patient was an outspoken example of the malady and suffered from outstanding local pressure symptoms in the form of severe headaches and bitemporal hemianopsia. In his paper Minkowski called attention to a case which had been reported two years before Marie's original paper by Fritsche and Klebs (11), who appear to have been the first to suspect the possible relationship of the disorder, which they considered to be one of pathological gigantism, with the ductless glands. Having found at autopsy an enlargement of both the thymus and hypophysis, they favored the former as the causative agent, and ascribed the enlargement of the pituitary to the general overgrowth of the body. They explained the fact, that this enlargement exceeded the relative proportions of other parts, on the grounds of the greater blood supply to the hypophysial region.

Minkowski was led to differ from these views of Klebs, having recently been impressed, as he said, by a lecture given by Virchow (1887), on the resemblance of the histological structure of the thyroid and pituitary glands. He argued from this that, since myxoedema is related to changes in the thyroid gland and is accompanied by trophic changes in the skin and extremities, acromegaly must be related to disturbances of the hypophysis since this disease, too, is evidenced by trophic disturbances.

On this weak link the pituitary gland seems first to have become associated with the disease acromegaly, but the exact nature of the disturbance of the hypophysis was barely guessed at.

Marie himself, under whose influence a thesis by his pupil Souza-Leite (15) appeared in 1890, including a summary of all the cases in the literature to date, 38 in number, was far from certain that the malady was due to a primary disturbance of the pituitary gland. Writing with Marinesco (16) in 1891, he summed up their studies of his first autopsy on an acromegalic, with the impression that they were evidently dealing with a general nutritional disease affecting especially the connective tissue of the extremities and certain organs and mucous membranes. The reason for this distribution of pathological changes,

he thought, depended upon the particular condition of the circulation and nutrition of the extremities and an embryological predisposition. From this point of view, he continued, the pituitary lesion might be considered simply analogous to any of the others, except for the fact that it is, first, a constant lesion, and second, not simply an interstitial sclerosis, but a hyperplasia of the follicles as well. He discarded as untenable the hypothesis of Klebs, that the thymus is responsible for acromegaly, or that the malady is primarily of nervous origin in accordance with the views expressed by von Recklinghausen.

In those days the question of whether the pituitary body had any function at all was still far from settled, and Marie was impressed by the recent experiments of Rogowitsch (22) in which an hypertrophy of the gland was shown to follow extirpation of the thyroid. It was the opinion of Rogowitsch that the thyroid and pituitary served to counteract various toxins of the body, and Marie came to believe that failure of the pituitary to function might permit these toxins to result in the occurrence of acromegaly in certain individuals with a special predisposition for the disease. Even as late as 1911, in a personal communication to Dr. Cushing, he stated that:

> "After having passed from one hypothesis to another, I find myself in no definite position regarding this question [hypo- or hyperpituitarism]. I wonder if the solution does not lie in a somewhat different direction. That is to say, that the important fact concerns itself less, perhaps, with the quantitative function of the hypophysis than with the modification and alterations of its secretions."

On the whole, however, Marie was apparently inclined, up to this time, to regard acromegaly as an under-function of the hypophysis, and it was this indeed which led Horsley and others to attempt pituitary extirpations in order, if possible, to reproduce the condition experimentally.

It had long before been pointed out by Virchow (1863) that the functioning pars-anterior cells showed under the microscope a distinct granulation of the protoplasm. In 1892 Massalongo (17), on an histological basis having found in a case of acromegaly a pituitary tumor consisting of granular cells, concluded that this malady was an expression of hyperfunction of the pituitary. He, too, in a manner similar to Fritsche and Klebs, believed that the thymus was responsible for the overgrowth, but assigned to the pituitary an equal and possibly a greater

share in this disturbance. This was the first expression in the literature against the somewhat tacitly assumed attitude that acromegaly was a disturbance of diminished activity of the gland. In 1894 Tamburini (25) described a case of acromegaly with autopsy findings, and clearly called attention to the hypertrophy of the epithelial elements of the pituitary gland, more specifically the chromophile cells. He concluded that the pituitary lesion was in the nature of an adenoma, but was different from adenomas in other glands in that it seemed to involve the entire organ—an assumption which is not borne out in most cases by later studies of other investigators. In an effort to explain the bizarre lesions of the hypophysis, said to have been found in cases of acromegaly, such as sarcomas and gliomas in earlier reports, he believed that the disease began with an overactivity of the chromophile cells of the anterior lobe and that later this overactivity, with its anatomical counterpart of chromophile adenoma, gave way to the degenerative lesions described by others, and that these were associated with clinical manifestations of underactivty of the gland, manifestations which were, to be sure, extremely vaguely sensed in his time.

In 1895 Brissaud and Meige (2) elaborated the views already expressed by Massalongo on the relationship and similarity between acromegaly and gigantism. In 1897 Sternberg (23) wrote an excellent monograph, bringing together all the data available in the literature then extant on 210 reports of trustworthy examples of the disease, and 47 reports of autopsies.

The logic underlying the belief that eosinophilic granules appearing in the cells of acromegalic hypophyses necessarily mean hyperfunction was placed on a more reasonable basis by the special work of Benda in 1900 (1) in demonstrating, in addition to his excellent preparations with special stains for granules, the fact that in young individuals during their growing period the eosinophilic granules are much more common than in older individuals, granular cells often extending into the tuberalis, and this occurrence being less and less common as age advances.

This disclosure was promptly recognized as of great significance, particularly in that it offered an explanation for acromegaly on a pituitary basis, even in the absence of an hypophysial enlargement or tumor. In discussion of a paper by

Benda on the subject, Virchow (1900) (27) stated that pathologists could no longer be content to regard a pituitary gland in acromegaly as normal on its gross appearance alone, but that the special examination for granules would have to be carried out. He stated further that in his collection there were five typically acromegalic skeletons with normal pituitary fossae, a fact which could no longer be regarded as incompatible with overactivity of the gland.*

Somewhat varied explanations of acromegaly have been advanced by others. In 1895 Campbell (5) considered the malady as a reversion to the anthropoid stage of development. Woods Hutchinson (1898) (12), one of the earliest American physicians to write about the disease, believed it to be a developmental disorder resulting in hypertrophy in those parts of the body corresponding to the areas of closure of the "ventral arches" of the embryo. Cagnetto in 1904 (3), on the basis of some clinical and pathological studies, expressed the view that it was not primarily a disease of hypophysial origin but that overgrowth and the hypophysial changes were both consequent to a general nutritional disorder. Accordingly, he was pleased to report in 1907 (4) a case of acromegaly which appeared to show at autopsy a pituitary tumor consisting entirely of chromophobe cells. He concluded that all that remained was for someone to find a chromophile adenoma without acromegaly, in order to complete the proof against the hypophysial origin of the disease.

In the same year (1907) Petrén (20) also expressed doubts as to the hypophysial origin of acromegaly, basing his opinion upon a personally observed case with a normal sized hypophysis and a coincidental syringomyelia. The latter finding led him to feel with von Recklinghausen (1890) (21) that the disease may be primarily of nervous origin. Indeed, also, in the same year, Magnus-Levy (13) wrote that: "neither pathological, experimental or clinical evidence exists to show with sufficient certainty that acromegaly is related to a change in the hypophysis, and assuming such a relation to exist, as most people believe,

*This statement one finds hard to believe in view of the fact that in the Brigham Hospital series of 100 cases of acromegaly the X-ray has disclosed an outspoken enlargement of the sella in all but seven cases. On this percentage basis Virchow would have needed to have skeletons of 71 acromegalics in his collection.

whether this change is one in the direction of increase or decrease of function."

Owing to the frequent and often very early disturbances of gonadal function in acromegaly, Stumme (1908) (24), Thumim (1909) (26), Mayer (1910) (18) and others believed that the primary disorder lay in the sex glands, and that this resulted secondarily in those changes of the hypophysis said to be characteristic of acromegaly.

There had been one most confusing fact, namely, the occasional report of cases of acromegaly in which not only was the hypophysis not enlarged but was said to be histologically normal. Erdheim, however, in 1909 (8) cast doubt upon all case reports of this kind by the report of such a case in which he had found a large, apparently separate eosinophilic adenoma, within the sphenoidal cells, supposedly having originated from an anlage of the craniopharyngeal pouch. This case aroused great interest and led, if to nothing else, at least to more careful examinations of the base of the skull in subsequent autopsies.

In 1909 also, Cushing (6) in his address before the Surgical Section of the American Medical Association, first employed the terms hyperpituitarism and hypopituitarism, the latter having been used for the states of experimental pituitary insufficiency which he with Crowe and Homans had been the first to produce or at least to describe. Since these experimental states of adiposity and sexual dystrophy resembled certain unexplained clinical syndromes accompanied by hypophysial tumor, acromegaly was regarded as in all probability the counter-state due to over-glandular secretion or hyperpituitarism. Three years later in his monograph on the pituitary disorders (7) Cushing assembled the arguments for his own belief in the hyperpituitary nature of acromegaly in the following manner:

1. "In the first place, in the only known conditions associated with skeletal overgrowth one usually finds an hypertrophic enlargement of the gland or a histologically demonstrable hyperplasia—primary in the case of acromegaly and gigantism, secondary in the case of eunuchism.

2. "Moreover, experimental extirpations of the hypophysis, with resultant glandular deficiency, have been shown to retard skeletal growth, and comparable effects are known, clinically, to be the consequence of glandular implication in tumor, injuries, or processes of disease in young individuals.

3. "Again, acromegaly tends in the long run toward a state which our experiments have shown to be brought about by glandular

insufficiency—adiposity, high sugar tolerance, and so on—and the fact that a low assimilation limit for carbohydrates characterizes the early stages of the disease suggests a coincident period of functional hyperplasia.

4. "Further, partial removals of the presumably hyperplastic pars anterior in certain cases of advancing acromegaly have led to seeming remissions in the symptoms, in the same way that partial removals of the hyperplastic thyroid in Basedow's disease induce remissions in the symptoms of hyperthyroidism."

Clinical and anatomico-pathological studies have continued with varying degrees of intensity up to the present time, but with perhaps no more advance than was made in these earlier years when the subject was of more universal interest than at the present. Dr. Cushing recognized at the time of his monograph that the solution would probably come from the experimental laboratory. He says:

"Experimental investigations, as we have seen, have thrown merely a negative light on the matter in so far as they have made clear that hypophysial deficiency—presumably of pars anterior—inhibits complete skeletal development; and it has been suggested that this may be due to a consequent lowering of the phosphorus and calcium content of the blood.

"So far as I am aware, there is only one certain experimental method of inciting skeletal overgrowth, namely, by early castration, and it is probable, after all, that, as Tandler suggests, the skeletal elongation characterizing eunuchism is merely an expression of a secondary hypophysial hyperplasia.

"No one has definitely succeeded in simulating a fixed state of functional overactivity of any member of the ductless-gland series, whether by feeding-experiments or by heterogeneous transplantations.

"Unquestionably there is some chemical process at work behind the actual glandular hyperplasia (Vassale, Cagnetto, *et al.*), and until this can be determined we must not only await the experimental reproduction of states of functional overactivity but must also continue to speak of the glandular change as the primary incident in the process."

This experimental proof which he felt was necessary for the final demonstration of the hyperactivity of the pituitary in cases of acromegaly and gigantism has finally appeared through the efforts of H. M. Evans and his co-workers (9) (10) at the University of California, where at last it was demonstrated that by the parenteral injection of an extract of the anterior lobe of the pituitary gland true gigantism can be produced experimentally in rats. Obviously the hormone which influences growth resides in this portion of the gland, and there are ample reasons to believe it is a function of the acidophilic cells, which are those chiefly composing the adenomas of acromegaly as Benda first pointed out. It only remains for some-

one by similar methods to produce the experimental counterpart of acromegaly. For this, some animal of a species in which, unlike the rat, the epiphysial growth of the bone ceases in the adult, will needs be employed.

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STUDIES IN ACROMEGALY
III. THE ANAMNESIS AND SYMPTOMATOLOGY IN ONE HUNDRED CASES

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INTRODUCTION

This study is based upon an analysis of the 100 cases which were discharged from the Peter Bent Brigham Hospital with the diagnosis of acromegaly, up to August 1, 1926. Nearly five times this number of patients with pituitary tumors have been studied here since the hospital was opened in 1913, but the 100 cases chosen for this analysis are those in which the acromegaly was paramount and unmistakable. We have purposefully avoided the inclusion of mixed types or borderline cases of dyspituitarism in which traces of acromegaly were discernible on histological or X-ray studies but which have become submerged in hypopituitarism.

Fifty-six of these 100 cases were primarily admitted because of the pressure effects of the acromegalic adenoma against the chiasm, and were operated upon for the relief of these symptoms. Sixteen others had either early signs of chiasmal pressure insufficient to warrant operation at the time, or signs sufficiently advanced to justify intervention which for one reason or another was postponed. In the remaining 28 cases there were no perimetric evidences whatsoever of chiasmal involvement.

Our material has the advantage of having been subjected to the relatively uniform management of a single clinic under the supervision of a single observer and within a period during which some notable advances in the knowledge of these disorders have been made. Inasmuch as all the reports in the literature are based on only a few personal observations, or on the data collected from the literature, it is hoped that some more clearly-

cut generalities may be deduced from this large and favorably studied group of cases.

INCIDENCE

The bizarre appearance which acromegaly lends to its sufferers, the mystery of its origin, the presentiment of scientists that its elucidation might provide a key to many endocrine problems—these and other factors have contributed to stimulate much work upon this subject. Yet the disease is a rare one—far more uncommon than other forms of pituitary disorder. Even in this particular hospital where, owing to an especial interest in the condition, acromegalics are frequently found, there have been only these 100 outspoken examples of the disease out of 50,000 patients admitted during the 12½ years under review, whereas the records show nearly 500 cases of pituitary disease of all sorts. Naturally, this being a surgical clinic, most of these patients are admitted because of tumor manifestations aside from other disturbances, and the surgically verified cases also show that the hypophysial adenomas *without* acromegaly are about five times as frequent as those *with* acromegaly.

Race. All of the patients in this series were members of the white race. Dana (1893) (11) reported a case in a Bolivian Indian. Yamada (1917) (31) described a case in a Japanese who was also suffering from beriberi; but a normal hypophysis was found at autopsy, and the published photographs of the patient's lower extremities are not convincing. A thorough search of the literature reveals only four examples reported as occurring in negroes [Berkley (4), Lackey (18), Krumbhaar (17), and Rake (27)], no one of which is strikingly acromegalic. Lackey's patient was a giant 8 ft. 6 in. tall, but with extremities and features in keeping with his race and great size.

The distribution among nationalities in our 100 cases was as follows: Forty-four Americans (native-born with Anglo-Saxon names), 21 Jews, 8 English, 8 Irish, 3 Germans, 3 Scandinavians, 4 Italians, 2 French, 1 Spanish, 1 Syrian, 1 Belgian, 1 Portuguese, 1 Armenian, 1 Hungarian, 1 Greek. The presence of 21% of Jews among our 100 cases is striking, for this proportion is, of course, far in excess of the relative number

of Jews in the American population (*viz.* 3.4%).* Similar observations have been made in regard to other endocrine disorders. Thus Lorand (1903) (20) in discussing the well-recognized frequency of diabetes among Hebrews, adds that acromegaly is also frequently seen among them, and quotes Maximilian Sternberg to this same effect. One wonders consequently whether the more highly strung, nervous make-up so frequently observed in members of this race is not associated with some instability in the endocrine mechanism.

Sex. Of our 100 patients, 44 were males, and 56 females. This seems to be an unusual preponderance of females in comparison with the findings of other observers, who usually cite the number of males as slightly in excess of females. Arnold (2), for example, found the proportion of males to females to be 55% to 45% out of 56 cases that he collected from the literature. Boyd (5), who gathered statistics on 65 cases, found 52.4% of these to be males and 47.6% females. A calculation on all the available case reports in the literature, exclusive of our own, makes the proportion of males to females 52% to 48%. It is obvious then, that the disease is equally proportioned between the sexes.

Age. The average age at which our patients came into the clinic was slightly above 40 years. The male patients averaged 33, and the female 45 years. Acromegaly, being essentially a chronic disease, however, the age of admission to the hospital can of itself have no significance except as a measure, roughly, of this chronicity.

Of far greater importance is the age of onset of the disease, and this unfortunately, is difficult to ascertain, for how is a patient to tell, even in retrospect, when such an ailment first made its appearance? The best one can do is to take as a starting point the age at which the patient first noted the presence of any of the symptoms known to be associated with the disease. On this basis it was estimated that the average age at which the malady began was 26.9 years. The actual range of ages was between 14 and 51, but by far the larger number fell into the third decade of life. This coincides very closely with

*In the last census (1920) the total population in the United States is given as 105,710,614, and the number of Jews as 3,600,350.

the figures in the literature, although the patient of Schultze and Fischer (29) began to show distinct acromegalic changes at the age of 11, and died at 15, of a large intracranial extension of her pituitary tumor. Other reports of so-called "infantile acromegaly" are rare, and not too convincing. The calculated onset in decades in this series as compared with that found by Sternberg (1897) (30) in 55 male and 70 female patients from the literature, is as follows:

	P. B. B. H. series: male and female	Sternberg: male and female
10 to 20 years of age	19%	14.4%
20 to 30 years of age	53%	52.0%
30 to 40 years of age	18%	25.6%
After 40 years of age	10%	8.0%

The disease, then, may be fairly stated to have its onset during the first half of adult life, and over 50% fall in the third decade.

Occupation. There was no undue proportion of individuals employed in what are known as the "dangerous industries." A slight preponderance existed of people engaged in professions or skilled trades.

FAMILY HISTORY

In four cases a definite history was obtained of acromegaly affecting a near relative (1 sister, 1 father, 1 uncle, 1 aunt). Twenty of the patients gave a history of having one or more near relatives who were either very noticeably large people, or had strikingly large hands, feet or features. This figure is conservative, for it includes only those cases in which the history definitely states that the matter was inquired into. Four patients had relatives who were abnormally fat. In two instances a member of the patient's family had diabetes, and one of the diabetics was insane. One patient had a father with progressive muscular atrophy; another patient, a woman, had a child much overgrown, apparently with pubertas praecox. A presumably negative family history with regard to acromegaly, or other endocrine or nervous disturbances existed in the anamneses of the remaining 68 patients.

The reports in the literature concerning this point are usually indefinite, but it is not uncommon to find accounts of acromegaly, gigantism or growth up to the maximum limits of normality, and of neuroses and psychoses affecting members of the patients' families.* While far from leading one to conclude that acromegaly is a familial disease, the information at hand at least suggests that certain propensities in a given family may become sufficiently exaggerated in one or two families to give rise to this condition.

MARITAL HISTORY

Only 64 of the 100 patients were married at the time of admission to the hospital, in spite of an average age of 40 years. Of the 44 male patients 26, or 59%, were married; and of the 56 females 38, or 68%, were married. The slight discrepancy

TABLE I

Effect of Acromegaly on Fecundity

	At time of admission	(average no. years married: 14.7)	
	Average no. pregnancies per marriage.	Average no. children per marriage.	Average no. miscarriages per marriage.
MALES			
14 males married 1-17 yrs. before the onset of symptoms.....	2.9	2.6	0.29
5 males married 1-7 yrs. after the onset of symptoms.....	1.4	1.2	0.2
5 males—relation of marriage to time of onset of symptoms unknown....	4.0	3.4	0.6
Total of 24 male patients with presumably healthy wives.....	2.8	2.5	0.33
FEMALES			
27 females married 1-20 years before onset of symptoms.....	2.0	1.05	0.48
9 females married 0-10 years after the onset of symptoms.....	1.1	0.88	0.22
Total of 36 females with presumably healthy husbands.....	1.8	1.38	0.41

*Fraenkel, Stadelmann and Benda's (1901) (16) second patient had a father, brother and sister, all of whom also had acromegaly.

may be accounted for by the corresponding discrepancy in the average age of the female patients (45 years) when admitted to the clinic, as compared to that of the males (33 years). Naturally the factors of race, social and economic standing, all have their particular modifying effects. But the chief factor in so small a percentage of marriages is undoubtedly the disease itself. Very few patients in whom the disease is full-blown marry, partly, no doubt because of their disfigurement, but largely because of the early secondary disturbance in the gonads.

The effect of the disease on fecundity is shown in table I.

It will be seen from this table that the average number of children in the families of these patients, particularly those who married after the onset of symptoms, is considerably restricted, especially in the case of the female patients.* Considering the marked disturbances in the sexual life of acromegalics—a point to be considered in detail later on—these facts could be readily anticipated.

PAST HISTORY

Development. Eighty-four patients gave a history of normal physical and mental development before the onset of the disease. Ten gave a history of excessive growth after the age of puberty (13-14 years). Two were said to have been noticeably backward mentally. Two patients reached maturity late in life (puberty at 20-22 years). Two patients were always small, weak and delicate before the first symptom arose.

Previous Illnesses. The incidence of serious diseases occurring at some time or another before the onset of the acromegaly did not seem greater among these patients than among persons generally of corresponding age. It may be noted that 26 of the patients had had antecedent operations: tonsillectomy 8, appendectomy 6, pelvic operations 5, etc.; also that 9 others gave a history of trauma—of the head in 6 instances; but none of these episodes appeared to be definitely associated in any instance with the onset of the acromegaly itself.

*The number of children per marriage in the United States is dependent upon such a large number of factors that no absolute figures are available for comparison, although statisticians assume as a working basis three children per marriage as a normal average.

Earlier writers have attempted to ascribe the disease to a variety of illnesses from which the patient was suffering previous to, or at the time of its onset. In our own series the following infectious diseases were recorded: Fifteen cases of scarlet fever, 12 typhoid fever, 6 diphtheria, 4 pneumonia, 4 influenza, 4 malaria, 3 otitis media (one with mastoiditis), 2 pleurisy, 2 meningitis, 2 syphilis, 2 smallpox, 2 acute rheumatic fever, and one case of pulmonary tuberculosis. It is difficult to believe, however, that any of these recorded maladies have any active etiological bearing on the disorder. In the majority of cases, namely 58, the earliest symptoms set in with no apparent stimulus. In only 14 did the onset coincide sufficiently closely with some preceding incident to suggest any relationship whatsoever. These may be listed as follows: In 3 cases it followed typhoid fever; in 2 cases a blow on the head; in 2 cases miscarriage; in 3 cases pregnancy; in 1 case cessation of nursing; in 1 case scarlet fever; in 1 case syphilis; in 1 case pleurisy with effusion.

In these few instances the patient had been in good health until the particular happening which supposedly was precursor to the endocrine disorder. In illustration, one patient was a Russian Jewess who was married, had borne two children, and enjoyed apparently perfect health until 29 years of age. Then, after a long siege of typhoid her menses became scanty and finally ceased. She remained weak and apathetic, gained weight gradually, and began to suffer from occasional frontal and suboccipital headaches, which progressively became more severe. Ere long the clumsy appearance of her hands and feet was called to her attention by her friends.

The literature contains many examples of this same sort, but it may be pointed out that in only three of the 12 patients in the series who had typhoid did the fever appear to closely precede the pituitary derangement. It is nevertheless of interest to speculate on the possible connection between infections and growth which seems to be especially active during the course

of typhoid fever. In exceptional instances this amounts to two or more inches of added height in a few weeks.* Rheumatic fever, syphilis, pleurisy and injuries, especially to the head, have also been frequently mentioned as causative agents. Even fright has been recorded as an etiological factor, as in Pel's (26) much-quoted case. Indeed, the variety of conditions, following which the symptoms of acromegaly may first appear, is evidence of the fact that no known disorder stands to the condition in the relation of cause and effect.

THE DISEASE ITSELF

Symptoms. The distinction between subjective and objective findings in acromegaly is particularly difficult to draw, for so many symptoms of the disorder belong to both categories; and it is not unlikely that many of the patients may have suffered from vague ill-health and have undergone profound changes in personal appearance, obvious to all others than themselves, before they recognized their disfiguration. That this might happen even in the case of a physician is recorded in Dr. Leonard Mark's autobiography of an acromegalic (22). The author had been a victim of the disease for many years before he accidentally discovered the nature of his malady. His friends, medical and otherwise, had meanwhile refrained from mentioning the subject, regarding his silence as evidence of sensitiveness, for they naturally thought he was aware of his condition.

The patients in this series appear for the most part to have had less considerate friends. Even so, a certain allowance must be made not only for the lapse of time between the actual onset of the disease and the recognition of certain symptoms, but also for the complete failure to recognize others that are less troublesome and less conspicuous. With these facts in mind, the symptoms and signs as recorded in the clinical histories have been assembled and are presented in table II in the order of their diminishing frequency.

Cf. "The Pituitary Body and its Disorders," pp. 236-237.

TABLE II

Symptoms and Signs of Acromegaly as Recorded in Clinical Histories

SYMPTOM	INCIDENCE
Enlargement of acral parts	100%
Enlargement of sella turcica on X-ray examination	93
Disturbances of menstrual cycle	87*
Headaches	87
Complete amenorrhoea	73†
Increased basal metabolic rate	70‡
Visual disturbances	62
Excessive perspiration	60
Hypertrichosis	53
Cutaneous pigmentation	46
Drowsiness and lethargy	42
Gain in weight	39
Diminished libido sexualis	38
Asthenia	33
Low blood-pressure (less than 120 mm. Hg. systolic)	30
Paraesthesia	30
Polyphagia	28
Fibromata mollusca of skin	27
Polydipsia	25
Enlarged thyroid gland	25
Glycosuria (diabetes mellitus 12)	25
Constipation	20
Vomiting	16
Rhinorrhoea	15
Photophobia	12
Uncinate attacks	7
Failing memory	7
Decrease of body hair	7
Persistent lactation	4
Failure of breasts to develop	4
Epistaxis	3
Choked discs	3

This formidable list of symptoms, especially when it is remembered that most of the less obvious ones actually occurred many times more often than would appear from the patients' own observation, indicates the far-reaching hold that acromegaly has upon the entire constitution of its victims. Unfortunately the pathological changes underlying many of these symptoms are obscure or quite unknown, but it is hoped that by reviewing them analytically, at least a tentative conception may be gained of the mechanism which results in this disease.

Acral Overgrowth. The typical and well-known changes in the features and extremities is of necessity present in all the cases, since not only the name but the clinical diagnosis of the disease, has, in the past at least, been based upon these

*Percentage of female patients.
†Percentage of female patients.
‡Percentage of 70 cases examined.

peculiarly localized manifestations of overgrowth. That this overgrowth, which as a matter of fact is a general and not a local process confined to the extremities, is related to a disturbance of the hypophysis can no longer be questioned; for although the many physiological activities of the gland remain imperfectly understood there is abundant evidence to prove that it is intimately related to the processes of growth. There is, in the first place, the negative evidence, brought out particularly by Fichera (1905) (15), Aschner (1909) (3), and others, that experimental hypophysectomy results in the stunting of growth. Then there exist numerous points of indirect evidence such as the enlargement of the pituitary in giants, and in castrated individuals that have grown beyond the usual size of their species. Moreover, it had long been observed that acromegalics whose disease began before the age at which closure of the epiphyses normally occurs were apt to be of particularly large stature. Brissaud and Meige (6), and others have gone so far as to say that acromegaly and gigantism were one and the same disease, the apparent difference depending entirely upon the age of onset.

The average height of our male patients whose disease began before 20 years of age was 6 ft. 2 in. (186 cm.), and the average height of the women in whom the same age relationship occurred was 5 ft. 6½ in. (166.25 cm.). The explanation of the continued growth even after the normal age for the cessation of this function has been ascribed by Dr. Cushing to the failure of the epiphyseal lines to close in these individuals.* Finally, H. M. Evans and his co-workers (13) (14) have succeeded in experimentally producing gigantism in rats, a species in which epiphyseal growth persists throughout life, by the injection of fresh anterior-lobe substance. Though the peculiar disposition of overgrowth in acromegaly has not been experimentally reproduced as yet, it may nevertheless be ascribed with full assurance also to a hyperfunction of the anterior lobe.

Disturbances of the Menstrual Cycle. As may be noted from table II, in 49 (87%) of the 56 female patients there existed a disturbance of the menstrual cycle amounting usually (in 73%) to a complete amenorrhoea by the time they first came

*Cf. the case of the giant, Turner, Case XXXII in "The Pituitary Body and its Disorders."

under observation. The early menstrual history seems for the most part to have been devoid of incident; the average age of onset of menstruation was 14 years. But the cessation of the menstrual cycle in the 41 patients in whom this had taken place occurred at an average age of only 31.4 years, with a distribution in decades as follows:

Before 20 years 3 patients ceased menstruating.
20 to 30 years 17 patients ceased menstruating.
30 to 40 years 10 patients ceased menstruating.
40 to 50 years 7 patients ceased menstruating.

Thus we see taking place in the female patients a pathological amenorrhoea at an age nearly 20 years younger than the average normal time of menopause which the recent studies of Dickinson and Pierson (12) put at 49 years.

The effect on the menstrual cycle may be presumed to be not simply an interruption of the local phasic changes in the uterus, but of the controlling ovarian function as well, for in none of our cases—and this is also true of studies by others—has any woman with acromegaly become pregnant in the presence of partial or complete amenorrhoea. It is also of importance to note in this connection that in six of our patients the disease dated from the time of pregnancy, after which catemenia never became re-established.

On the other hand, 13% of our female patients continued to menstruate quite regularly in spite of advancing acromegaly; one or two of them even bore children. We have one case (Surg. No. 4465) whose disease began at the age of 27 with amenorrhoea. At 31 she was operated on by Dr. Cushing, who partially extirpated an eosinophilic adenoma of the pituitary by a transphenoidal operation. Her vision improved and her headaches ceased. Four years after her operation she began to have profuse uterine bleeding. The cause of hemorrhage was discovered to be a cervical polyp, which was removed by operation, and following this operation, after 8 years of amenorrhoea, regular periods were re-established.

The frequency of premature cessation of menstruation occurring, as will be shown later on, so early in the disease, would at first sight appear to be incompatible with the conception of

pituitary hyperactivity, for it is well known that in another and far more common type of pituitary disorder termed hypopituitarism, which is taken to be the exact antithesis of acromegaly though also due to an adenoma of the gland, amenorrhoea is an even more constant early symptom.

But here again the experiments of Evans and his associates have thrown light on the subject. Their injections into female rats of anterior-lobe pituitary substance were originally made for the sake of studying the effects upon the oestrous cycle, and it was soon discovered that the hypophysial extract very promptly interrupted this cycle. Later, however, in examining the ovaries of animals so treated, instead of finding shrunken, fibrosed organs, the ovaries were found to be actually larger than normal ones, and owing to their irregular surfaces were termed "mulberry ovaries." On microscopic examination these irregularities proved to be corpora lutea, each containing an undischarged and degenerated ovum.

Unfortunately there is no record of a satisfactory examination of the ovaries of a female acromegalic who was sufficiently young to have disclosed a condition—if indeed such a condition exists—analogous to the mulberry ovary produced in Evans' experimental animals. In any case, the frequent and early cessation of the menstrual cycle in acromegaly is so comparable to a similar effect produced upon the oestrous cycle of the rat by an excessive supply of anterior-lobe substance that a similar cause may certainly be assumed to be at work.

Headache. The headache in acromegalic patients may be due to factors additional to that of increased pressure within the pituitary capsule, for among our cases there have been some who were entirely free from headache and who nevertheless showed a very large sella turcica, and others whose chief complaint was headache, sometimes most persistent and excruciating in nature, and yet by X-ray examination proved to have a small, or relatively small, sella. Indeed in one case with extremely severe headaches an autopsy showed a pituitary of practically normal size. However, the fact that out of the 13 patients in the series who were free from headaches 9 showed no visual-field defects, would seem to support the view that headache is probably due in the majority of cases to the intra-

capsular pressure from the enlarging gland. This at least appears to be true of the cephalalgia in patients with hypophysial adenomas unassociated with acromegaly, for by the time the sella has become fully ballooned the discomforts usually cease.

In this connection it may be pointed out that only 7 of the 100 cases showed sellar outlines which in profile could be considered to be of normal dimensions; all the others showed varying grades of sellar enlargement in spite of the fact mentioned above, that 28 of them were not operated upon because of the absence of demonstrable perimetric defects in the visual fields.

Visual Disturbances. These, as described in detail by previous observers from this clinic (10) consist usually of symmetrically disposed defects in the fields which progress downward until the typical bitemporal hemianopsia or even a more advanced stage of the process is produced. The cause of these changes is obviously due to upward pressure against the chiasm of the extending gland, which may ultimately rupture the capsule with marked intracranial extension of the lesion. This intracranial extension at times may pass through the capsule to one side rather than in the midline, and two of the cases in the series showed a homonymous rather than a bitemporal hemianopsia. Such a lateral expansion of the intracranial process naturally enough may lead to pressure upon and irritation of the uncus and produce the uncinate attacks, which, as mentioned in the table, were recorded in seven cases.

Needless to say, these disturbances of vision are accompanied by a primary optic atrophy which may go on to produce complete blindness. Rarely does a choked disc occur. In only one case in the series was it marked, though in two others a slight papilloedema was recorded. In all these instances there was evidence of marked intracranial extension of the process leading to general pressure symptoms, with vomiting and so on, such as one may see in a larger percentage of patients with chromophobe adenomas associated, from the onset, with pituitary insufficiency and without any trace of acromegaly.

Summarily then, in addition to the disturbances in the glandular activity of the pituitary which occurs in all cases of acromegaly, an enlargement of the gland took place in 93% of this series. This enlargement was accompanied at times by

headaches alone, at others only by visual-field defects, but in the majority of cases by both. With all due emphasis, however, on these symptoms attributable to local pressure, it must be borne in mind that outspoken acromegaly may occur in the absence of any clinical evidence of a demonstrable enlargement of the hypophysis.

Drowsiness and Lethargy. These are difficult symptoms to estimate. They are much more common in cases of pituitary insufficiency, yet strangely enough occurred in 42% of these acromegalics, and were often marked, in spite of advanced hyperpituitarism. In a few of these patients, the presence of an intracranial extension of the tumor may have been responsible, but in the greater majority these peculiar complaints remain for the present unexplained.

Cutaneous Manifestations. Among these may be considered the symptoms which have been tabulated under hypertrichosis, excessive perspiration, cutaneous pigmentation, fibromata mollusca, loss of hair, and so on. It is safe to say that many of these may be ascribed to the hypophysial derangement and may well enough represent the hypertrophic changes of the cutaneous appendages. The hypertrichosis, for example, is often striking. The hair of the scalp, pubes and axillae is not especially affected in quantity, but the remainder of the body becomes extremely hairy, even in women, who often tend to develop beards. But even more noteworthy than the amount and distribution, is the quality of the hair, which is thick, wiry and oily. Moreover, it has its reverse picture in the delicate, fine, silky hair of the head, and comparative hairlessness of the body, in persons the victims of pituitary insufficiency from adenoma or other causes.

In the same way the enlarged sebacious and sudoriferous glands may account for the excessive sweating and oiliness of the skin, and thus for the peculiar disagreeable odor which frequently surrounds acromegalics. Although proof of this hypertrophy exists by miscroscopic examination, it is hardly necessary, for the large widely open pores visible on inspection of the skin of one of these patients appears like an equal area of normal skin viewed through a magnifying glass. The dry, soft,

thin, delicate skin characteristic of patients with hypopituitarism is again confirmatory by contrast.

In 27 cases the presence of fibromata mollusca was mentioned, and one or two of the patients have been sufficiently annoyed by these cutaneous tags to have some of them surgically removed. Histologically, of course, these, too, are but an expression of local hypertrophy of subcutaneous fibrous tissue.

In a few other patients there have been small subcutaneous lipomata, and in one patient a large lipoma of the back. What bearing this may have, if any, on adiposity, is not clear. There are frequent statements made in the histories, regarding ravenous appetites, and the early gain in weight is undoubtedly due largely to increase in massiveness of the body, but certain of these people later on become distinctly adipose and give the impression of losing some of their acromegalism and suggest more the picture of cases of pituitary insufficiency, though of course the bony changes once established are never lost. The occasional transition from hyperactivity to insufficiency of the pituitary gland may also account for the seven patients who were found to have a distinct decrease of body hair.

Brown pigmentation of the skin occurred in 46 patients; the significance of this also must remain essentially unexplained. But the presence of asthenia in 3 cases and a distinctly subnormal blood pressure in about an equal number would suggest some interference with adrenal activity.

The pain, tingling and numbness of the extremities that we have grouped under "paraesthesia" are again but poorly understood except that they probably have some relation to the pituitary hyperactivity, for these symptoms have been observed frequently to disappear immediately after operation. The attempt occasionally met with in the literature to interpret the paraesthesia to a pinching of the nerve trunks by the hyperostoses surrounding the intervertebral formania, is untenable, not only because of the improvement shown immediately after operation which cannot affect the hyperostoses so quickly, but also because one patient, whose skeleton has been preserved here, and which shows most extensive hyperostoses of the entire osseous system, never complained of paraesthesia. On the other hand, the hypertrophy of the lamellar sheaths with actual de-

generation of the nerve endings first described by Marie and Marinesco (24) may very readily be, in part at least, responsible for this type of discomfort.

Polyglandular Disturbance. There remain certain of the recorded signs and symptoms which may, for lack of better grouping, be brought together under this heading. The association has been touched upon above, in hinting at the possible relation of the pigmentation and asthenia to an adrenal participation. It is the opinion of this clinic that of all the ductless gland disorders, acromegaly (hyperpituitarism) shows grossly a more widespread involvement of the other endocrine glands than is true of any other primary derangement of one member of the series. A palpable or definitely enlarged thyroid, for example, was recorded in 25% of the patients. In one or two of them the goitre was so large as to cause dyspnoea and necessitate operation. In three cases hyperthyroidism was suspected and a subtotal thyroidectomy performed, the gland in each case proving to be merely of a colloidal type. Glycosuria was recorded in 25%; and the inevitable disturbance of the function of the sex glands has already been dealt with.

Just what may be the relation of acromegalic diabetes to true pancreatic diabetes, and the changes in the thyroid to the alterations in the basal metabolic rate (9) is not as yet determined. Though these matters will be more fully considered in subsequent papers in this series, certain facts in relation to them may be here briefly set down. The first concerns the question of:

Metabolism. It may be stated in brief that in patients with acromegaly the basal metabolic rate is usually above normal and sometimes markedly above normal, whereas in patients with the more common chromophobe type of pituitary adenoma unassociated with acromegaly it is almost inevitably subnormal. Of the 73 patients in whom the rate was tested 50 were above normal, the highest recorded rate being +61%. In 23 cases it was below normal, the lowest being —17%. These figures are in marked contrast to those in patients with pituitary lesions unassociated with acromegaly in which registrations of —30% to —40% are common. The acromegalics with enlarged thyroids that happened to have their metabolism studied proved

to fall into the group with rates registering above zero. Studies of this subject which will be detailed elsewhere show, nevertheless, that the hypophysis is primarily responsible for the disturbance of metabolism.

Glycosuria and Carbohydrate Tolerance. Twenty-five patients gave a history, or proved on examination of the urine, to have glycosuria. Of these, 12 had definite clinical diabetes mellitus, the others only a transient glycosuria. Fasting blood-sugar determinations, moreover, in a dozen other members of the series without glycosuria showed the sugar percentage to vary between 0.11%-0.16%; that is, approaching the upper limits of normal. This relatively large number of acromegalics showing sugar in the urine, and the fact that out of five times as many patients with hypopituitarism in the records of this hospital, only two or three showed glycosuria, makes it evident that this tendency toward decreased tolerance for sugar is not a mere coincidence.

The general subject of the carbohydrate metabolism as affected by acromegaly will be taken up in another communication. Suffice it to say that even evident clinical diabetes mellitus in patients also suffering from acromegaly frequently behaves in unexpected ways. Some data exist in our records, moreover, showing that reduction in hypophysial activity, as by partial removal of the pituitary tumor, results in an improved tolerance for sugar, thus suggesting that directly or indirectly hypopituitarism favors diabetes.

Further Symptoms. Persistent lactation over a period of years occurred in four female patients. It consisted in the presence of small quantities of yellowish fluid resembling colostrum evident on compression of one breast in three of the patients and both breasts in the fourth.

Brown (1925) (7) refers to a woman with "pituitary tumor" (presumably acromegalic) who had been lactating continuously for seven years. Roth (1918) (28) reports a case of acromegaly in a male patient in whom a secretion from the left breast became established which microscopically and clinically proved to be milk. A woman seen in the Brigham clinic, since the 100 cases forming this study were assembled, has been lactating without interruption for five years following a second

pregnancy, since when her acromegaly became manifest, and menstruation has not been resumed.

The studies of Miss Lane-Claypon and Starling proving the stimulating effect upon lactation of foetal tissue juices is evidently insufficient to explain the acceleration of mammary development and lactation in every case. Ancel and Bouin (1909) (1) have shown in their experiments upon rabbits that the stimulus in this animal at least arises from the corpus luteum, whether that of pregnancy or "pseudo-pregnancy." Leo Loeb (1917) (19) has proved this to be the case in guinea-pigs and has shown that when the entire ovaries or the corpora lutea alone are removed during pregnancy in this animal the mammary tissue fails to proliferate even though the pregnancy continues uninterruptedly to term. All this suggests that mulberry ovaries with persistent corpora lutea such as Evans sees in his giant rats may conceivably occur in some amenorrhoeic acromegalics and stimulate the secretion of milk.

The part played by the posterior lobe on milk secretion is believed by Sharpey-Schafer to be simply a stimulus to the smooth muscle-fibres of the mammary ducts. So far as the anterior lobe is concerned, Marshall (1922) (25) states that lactation may be prolonged for an almost indefinite period after ovariotomy, which as is known causes a secondary hypertrophy of the pituitary body. Hence he believes it to be not unlikely "that these two facts are correlated, and that after the removal of the ovaries the function of the corpus luteum in relation to milk secretion may be taken over vicariously by the pituitary." In the case of acromegaly mentioned above as having been too recently admitted to the hospital to be included in this series, in which lactation and amenorrhoea have persisted for five years, a report from a surgeon who had occasion to observe and to incise her ovaries during an abdominal operation, two years ago, states that "both ovaries were in a state of semi-atrophy without signs of ovulation."

The physiology of lactation even in normal individuals is evidently so poorly understood that an effort to explain it under these already complicated circumstances cannot be more than speculative. More readily comprehensible is the failure of the breasts to develop. This occurred in four young women whose

disease began at puberty and whose ovaries must, therefore, have become involved too soon to exert their influence upon the development of these secondary sex-characters.

Three patients, all of them female, had occasional free epistaxis, but in only one did this occur sufficiently periodically to have been regarded in the light of vicarious menstruation.

CHRONOLOGY OF SYMPTOMS

With complete understanding of the uncertainty attached to the treatment of data obtained from the anamnesis, we have nevertheless attempted to formulate a table of symptoms in the chronological order of their appearance, hoping that the preceding analysis of the symptoms and their origins may help us to follow the course of the disease.

TABLE III
Time of Appearance of Symptoms

SYMPTOMS.	verage duration in yrs. at time of admission.	Percentage of cases where it appeared as one of the initial symptoms.	Percentage of incidence.
Gigantic stature (6 ft. [180 cm.] or over)	14.7	10.0	14.0
Irregular menses	10.5	26.8 (% of female patients)	42.8 (% of female patients)
Gain in weight	9.3	20.0	39.0
Increase in size of hands and feet	8.4	48.0	100.0
Coarseness of features	7.0	37.0	100.0
Complete amenorrhoea	6.4	26.8 (% of female patients)	73.0 (% of female patients)
Increased body-hair	6.3	7.0	53.0
Paraesthesia	5.7	11.0	30.0
Headaches	5.5	27.0	87.0
Drowsiness	4.9	6.0	42.0
Failing vision	4.1	10.0	68.0
Polyphagia	4.1	1.0	28.0
Excessive perspiration	3.7	3.0	60.0
Asthenia	3.6	5.0	33.0
Polydipsia	3.4	2.0	25.0
Diminished libido sexualis (male patients)	3.0	4.0	38.0

In table III are presented in as nearly a summary fashion as possible what seem to be almost constant features of the *onset of the disease,* as case after case is studied in the present series, and in the literature wherever complete data is presented, namely.

1. An early period during which growth becomes accentuated, always expressed in an increase in the size of the acral parts and usually also of the entire body, especially the bony framework, sometimes amounting to actual gigantism, which is naturally accompanied by a gain in weight. This period is also characterized in the women by irregularity of the menstrual cycle or complete amenorrhoea.

These symptoms we have already seen in all likelihood associated with overactivity of the *pars anterior* of the pituitary gland. They are the most constant symptoms and are in the majority of cases the first manifestations of the disease, which may, therefore, be fairly assumed to begin with a hyperactivity of the gland.

2. Then follows a second period characterized by neighborhood symptoms resulting from pressure of the enlarging adenoma which occurs, in those cases where it is present, on the average of not until 3 to 6 years after the onset of the disease. In our patients, for example, 68 were suffering from failing vision at the time of admission to the hospital, but only 10% gave this as one of the earliest manifestations of their difficulties, and even in these 10% it is not inconceivable that a gradual increase in the size of the extremities may have gone unnoticed while the very first evidence of failing sight would, as a rule, have aroused the patient's apprehension immediately, and the time of its appearance be clearly recalled.

As noted beforehand, tumor symptoms are, subjectively at least, absent in a fair proportion (28%) of these cases, although the X-ray may usually (93%) detect an increase in size of the sella. It is true, nevertheless, that symptoms of hyperactivity very frequently begin before any evidence of pituitary enlargement exists, and may indeed run its course to full-blown acromegaly without any signs of tumor ever appearing on clinical or even X-ray evidence.

3. There is a final or third period when patients ordinarily first come under observation in which they show a con-

glomeration of secondary symptoms and signs indicative of the more far-reaching effects of the disorder ascribable partly to the late effects of visceral splanchnomegaly (cardiac in particular) and partly to a secondary effect of the other endocrine organs. Such evidence as glycosuria, to be sure, naturally remains unobserved by the patient and is, therefore, not discovered until clinical examination reveals it. On the other hand, the relatively late appearance of symptoms like polyphagia with especial appetence for sweets, polyuria, and polydipsia, would suggest a correspondingly delayed involvement of the glycolytic function of the body.

Thus we may say that acromegaly is a disease which begins with hyperactivity of the pars anterior of the hypophysis, which usually enlarges and forms a tumor, and as the disease advances other organs, but primarily the endocrine system, become involved in the disease.

SUMMARY AND CONCLUSIONS

An analysis of 100 consecutive cases of acromegaly observed at the Peter Bent Brigham Hospital during the years 1913-1926 has been undertaken, chiefly from the standpoint of the anamnesis.

Only two out of every 1,000 patients admitted to the hospital, and approximately one in every five with a diagnosis of pituitary disorder, presented this condition.

All the patients belonged to the white race. Twenty-one per cent were Jewish.

The relative incidence between the sexes is probably about equal.

The disease begins most commonly between the ages of 18 and 35 years, with an average age of onset of 26.9 years.

Certainly hereditary influences exist as shown by the fact that a family history of acromegaly in 4% of the cases, and in 20% a family history of noticeably large individuals was recorded.

The fecundity of the patients was below the usual average, and the number of children born to those who married after the onset of symptoms was small.

The anamnesis revealed no unusual susceptibility to any group of diseases or to any particular type of accidents. In the women the catamenia became established at an average age of 14 years, but cessation of menstruation occurred at an average age of only 31.3 years.

A very large number of symptoms were recorded, pointing to the far-reaching effects of this disease. The more important of these symptoms have been especially considered in their relationship to the seat of the underlying pathological changes.

From all this it would seem that the part played by the *pars anterior* of the hypophysis is undeniably one of primary importance. Its exact rôle is not yet entirely clear, but the hypertrophic changes so characteristic of the disease, occurring as they do in people at least half of whom have reached a maximal or even excessive stature before the apparent onset of the malady, are thought to signify a pathological hyperfunction of this gland which not only initiates the process but continues perhaps with varying intensity, throughout the course of the illness.

Usually the overactivity of the gland is followed by a tumor formation giving rise to pressure symptoms such as headache, bitemporal hemianopsia, and primary optic atrophy.

Finally other symptoms develop, which are obviously of a secondary nature. They are associated with a general splanchnomegaly with a profound disturbance of the reproductive glands, and with evidence of secondary involvement of other of the endocrine organs.

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DEPRESSOR EFFECT OF TISSUE EXTRACTS
THE DEPRESSOR EFFECT OF CERTAIN TISSUE EXTRACTS

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In 1896 Schäfer and Moore (1) while investigating the contractility of the spleen, noted that a fall of blood pressure usually followed the injection of brain extracts, and in 1899 Mott and Halliburton (2) suggested that the active substance was choline.

Osborne and Vincent (3) showed in 1900 that extracts of nervous tissues cause a fall in blood pressure, which is obtained after section of both vagi and after full doses of atropine. On the same date there appeared a communication by Halliburton (4) in which similar results were announced, but with the important difference that neither nervous tissue extracts nor choline produce a fall after atropine.

Vincent and Sheen (5) in 1903 showed that the depressor effect is obtained after injection of extracts of all tissues except the chromaphil. They found that, as in the case of nervous tissue extracts, extracts of other organs contain some depressor substance which is not choline.

In regard to the posterior lobe of the pituitary body, it was found by Schäfer and Vincent (10) that a depressor substance is present. A depressor effect is always obtained as a result of a second dose, the pressor effect being then absent. This depressor effect is not abolished by atropine, as that of choline is. Therefore the depressor effect of posterior lobe of pituitary is not due to the presence of choline. It was also shown by Schäfer and Vincent that the depressor substance is contained in the alcohol extract and can be removed by thorough extraction with alcohol. Recently Sharpey-Schafer and Macdonald (11) have shown that the substance in question is histamine, and the same view is expressed by Sharpey-Schafer in

his book on the Endocrine Organs, published in 1926 (Second Edition).

Few attempts to isolate the active principle or principles have been made. In 1903 Vincent and Cramer (6) isolated from nervous tissue extracts a substance which seemed to be a dicholine anhydride, while more recently, in 1926, Dale and his co-workers (7) after tedious and complicated processes have isolated histamine from ox liver. Although Dale's work tends to support the theory that tissue extracts owe their depressor activity to their histamine and choline content, certain results we have obtained indicate that other factors are involved as well. A preliminary communication was made in the Lancet by us on this subject (12).

PREPARATION OF EXTRACTS

The extracts employed were made from the tissues of cats, rabbits, and occasionally of guinea-pigs.

1. *Saline Decoction.*

A weighed quantity of fresh moist tissue was ground in a mortar with sand, five times as many cubic centimetres of 0.9% normal saline solution being added as there were grammes of moist tissue; after thorough trituration the mixture was boiled with the addition of a few drops of dilute acetic acid. It was then filtered and the filtrate, after cooling, and refiltering if necessary, used for injection. In addition, portions of saline extracts were subjected to Pasteur-Chamberland filtration and further portions to shaking with benzene, as recommended by Pickering for removal of phosphatides.

2. *Alcoholic Extract.*

The fresh moist tissue was pounded in a mortar with absolute alcohol and sand and left in contact with alcohol for some hours. The mixture was then filtered, the filtrate evaporated to dryness, and the residue taken up with 0.9% saline, five times as many cubic centimetres of saline being used as there were originally grammes of tissue. The fluid was again filtered and used.

3. *Ether-Extract.*

This was prepared in a way similar to that for the alcoholic extract, except that methylated ether was used instead of alcohol as the extracting agent.

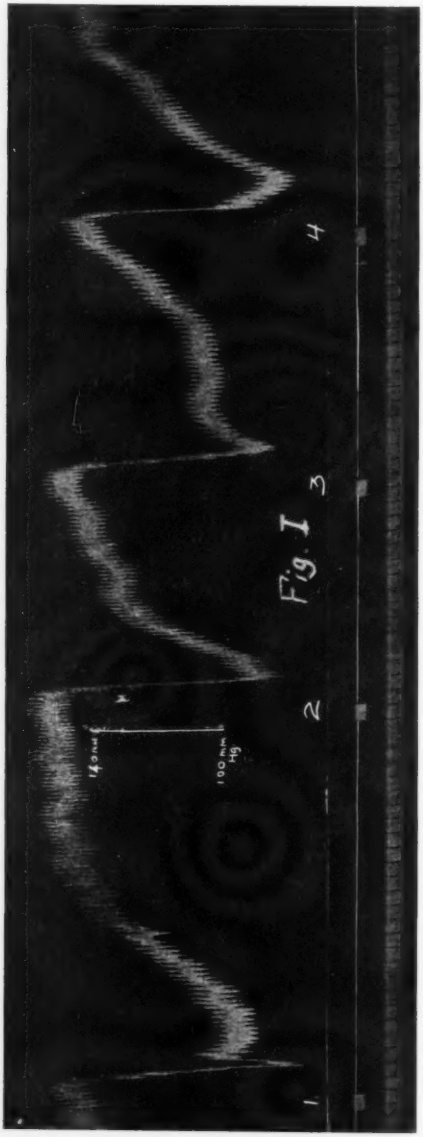

Fig. 1—Cat. Ether. Time in seconds and ten seconds. (1) 10 cc. saline extract of muscle. (2) 10cc. saline extract of lung (3) 10cc. saline extract of liver. (4) 10cc. histamine-choline solution. (0.1 mgm. aa.).

4. *Alcohol-Ether Extract.*

This was prepared by subjecting the residue after evaporation of the alcohol to the action of ether, then evaporating the ether after filtration, and taking up with saline as above. Solutions were prepared containing 0.01 mgr. of both histamine and choline in 10 c.c. of saline, and also solutions of 10 times the strength.

Methods.

Cats and rabbits were employed for the experiments. Anaesthesia was induced and maintained by ether.

The blood pressure was recorded from the carotid artery in the usual way by a mercury manometer. The vein used for injection was either the external jugular or the femoral.

The injections were made at room temperature, in 10 c.c. doses, which were given at the rate of 1 c.c. per second.

PHYSIOLOGICAL EFFECTS

Comparison of saline extracts and histamine-choline mixtures:

A. *In Cats.*

A striking resemblance is found between the curves produced by the injection of tissue extracts and histamine-choline solutions. In all cases there is a sudden fall with a more or less prolonged recovery. Results such as shown in Fig. 1 make it tempting to put forward the suggestion that tissue extracts owe their depressor effect to a mixture of histamine and choline.

B. *In Rabbits.*

Dale and Laidlaw (8) in 1910 showed that rabbits are peculiar in their reaction to histamine. If they are anaesthetized sufficiently to paralyze the bronchial muscles, histamine produces only a rise of blood pressure even in doses which would induce profound, even fatal, shock in a cat. Short of this stage of anaesthesia, considerable doses of histamine produce pulmonary constriction and usually a fatal spasm of the bronchial muscles which offers great obstruction to the entry of air. Dale and Laidlaw used urethane, but in our experiments it was found that 30-45 minutes of ether anaesthesia gave a condition in which histamine produces a rise of blood pressure.

It is obvious then that we have in the rabbit a most suitable animal for investigating the effect of tissue extracts and testing the histamine-choline hypothesis.

In rabbits under these conditions all tissue extracts produce a fall of blood pressure (Fig. 2), which is little, if at all, affected by atropine, while mixtures of histamine and choline produce either a small fall followed quickly by a rise or a pure rise before atropine, and always a rise after atropine (Fig. 3).

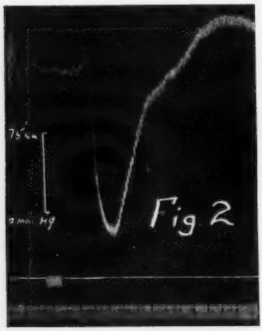

Fig. 2—Rabbit. Ether. 10cc. solution of brain. (Before atropin.)

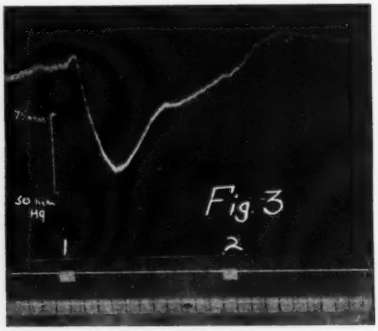

Fig. 3—Rabbit. Ether. (1) 10cc. saline extract of liver. (2) 10cc. histamine-choline solution. (0.1 mgm. aa.). (After atropin.)

The use of the rabbit eliminates the fall due to histamine, and atropine abolishes the depressor effect of choline; yet in the rabbit after atropine, in doses sufficient to abolish the action of the vagus as judged by direct stimulation, saline extracts of tissues produce a pronounced fall of blood pressure (Figs. 4a and 4b). Hence there would seem to be some substance contained in tissue extracts differing in its pharmaco-dynamical and chemical properties from both histamine and choline (Figs. 5 and 6).

In the course of our experiments we had been constantly hindered by clotting in the cannula (though we were using the usually very efficient saturated sodium bicarbonate solution), especially during the injection of saline extracts. In one case at the end of an experiment we injected the usual dose of a fresh saline liver extract, more rapidly than usual, with the result that the rabbit died at once. On opening the heart im-

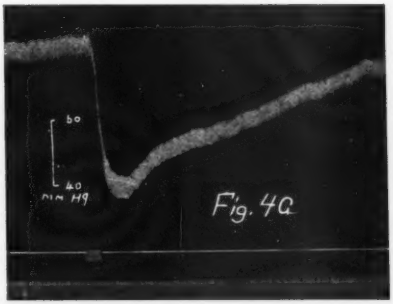

Fig. 4a—Rabbit. Ether. 10cc. saline extract of brain. (Before atropin.)

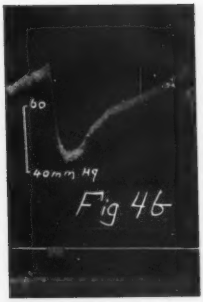

Fig. 4b—Rabbit. Ether. 10cc. saline extract of brain. (After 3cc. 1% atropin.)

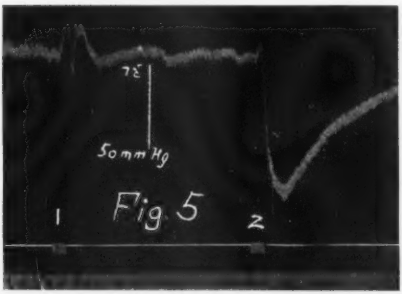

Fig. 5—Rabbit. Ether. (1) 10cc. histamine-choline solution. (0.1 mgm. aa.) (2) 10cc. saline extract of brain.

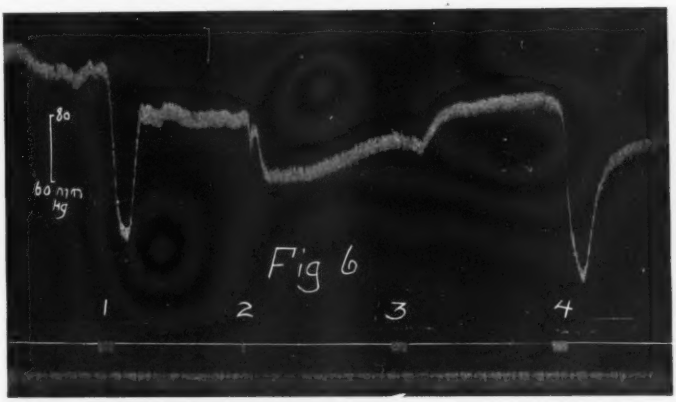

Fig. 6—Rabbit. Ether. (1) 10cc. saline extract of liver. (2) 3cc. 1% atropin. (3) 10cc. saline-ether extract of brain. (4) 10cc. saline extract of liver.

mediately, the right auricle and ventricle and pulmonary arteries were found full of thrombus.

Burke and Tait (9) in 1926 had meanwhile published the results of an investigation into the effect of tissue extracts on the coagulability of the blood, and as they showed that pulmonary thrombosis and embolism are of such frequent occurrence after the injection of tissue extracts, it seemed to us that here might be found the explanation for the fall of blood pressure produced in rabbits by tissue extracts, especially as rabbits were known to be unusually susceptible to intravascular clotting.

To eliminate the factors producing thrombosis we adopted the course advocated by Burke and Tait, viz., Pasteur-Chamberland filtration, which, as they showed, completely deprives an extract of its power to produce intravascular clotting.

Using this extract in rabbits and comparing its effect with that of the same extract treated in the ordinary way, we found that the fall of blood pressure is still obtained in both cases before or after atropine (Fig. 7).

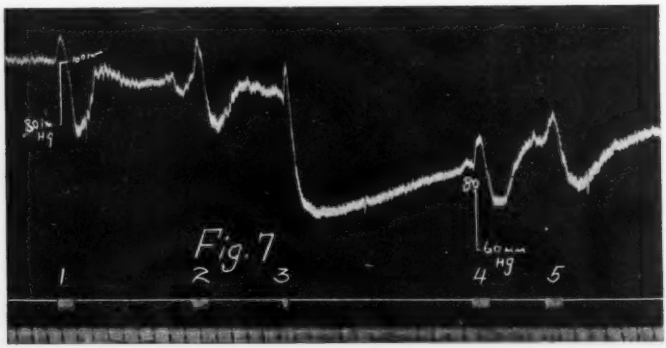

Fig. 7—Rabbit. Ether. (1) 10cc. Pasteur-Chamberland filtered saline extract of liver. (2) 10cc. saline extract of liver. (3) 4cc. 1% atropin. (4) 10cc. Pasteur-Chamberland filtered saline extract of liver. (5) 10cc. saline extract of liver.

A further procedure recommended to us in conversation by Dr. J. W. Pickering for ridding the extract of phosphatides was shaking with benzene. Here again using a tissue extract which was divided into two parts, one being shaken with benzene, little or no difference was observed in the effect of their injection on the blood pressure of the rabbit (Fig. 8).

It seems then that obstruction in the pulmonary circulation is not necessarily responsible for the fall of blood pressure produced by tissue extracts.

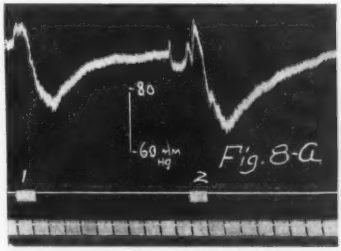

Fig. 8a—Rabbit. Ether. (1) 10cc. saline extract of muscle, shaken with benzene. (2) 10cc. saline extract of muscle. (Before atropin.)

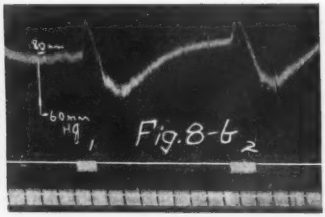

Fig. 8b—Rabbit. Ether. (1) 10cc. saline extract of muscle, shaken with benzene. (2) 10cc. saline extract of muscle. (After atropin.)

Effects of Alcohol-Ether Extracts.

As shown by Vincent and Sheen, a certain amount of depressor substance is soluble in ether after extraction with alcohol, though none is directly extracted by ether.

The active substance which goes into solution in ether consists apparently to a great extent of choline, as the depressor effect is nearly always abolished by atropine (Fig. 9a).

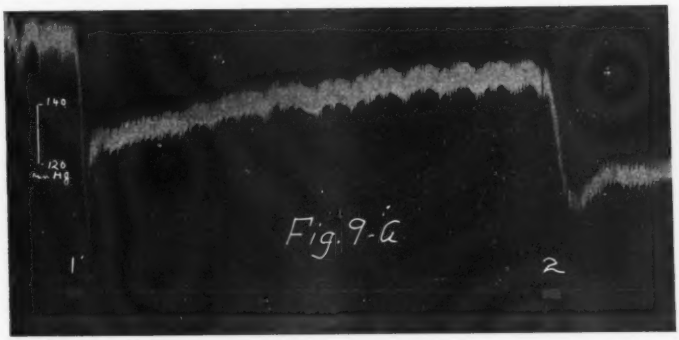

Fig. 9a—Cat. Ether. (1) 10cc. saline extract of liver (after Pasteur-Chamberland filtration). (2) 10cc. saline extract of liver.

A point of some significance is the level of the pressure at the time of injection. Using a cat with a blood pressure of

about 150 mm. Hg., a considerable fall of pressure is obtained on the injection of saline extracts of liver. If some hours later the animal is decerebrated so that its blood pressure is now about 40 or 50 mm. Hg., the injection of 10 c.c. of the same tissue extract produces merely such a rise as is produced by an equal quantity of saline. (See Fig. 9b.)

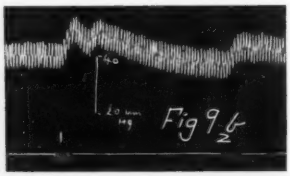

Fig. 9b—Cat. Decerebrated. Two successive injections 10cc. saline extract of liver.

In an animal whose blood pressure is low, saline usually produces a rise, though it fails to do so when the pressure is already high. These results have been obtained repeatedly.

SUMMARY

The depressor effect of tissue extracts cannot be accounted for on the assumption that their action is due solely to their histamine and choline content.

The fall of blood pressure produced in the rabbit is not due to temporary obstruction in the pulmonary circulation.

Tissue extracts do not produce a fall of blood pressure when the initial pressure is low (30-40 mm. Hg.).

The expenses of this research were defrayed in part by a grant to one of us from the Government Grant Committee of the Royal Society.

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HYPERNEPHROMA IN A HORSESHOE KIDNEY

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Horseshoe kidney is not a rare anomaly. It was found once in every 142 operations on the kidneys at the Mayo Clinic[1], while Carlier and Gérard[2], in the extensive compilation of statistics from the literature of the world, collected 81 cases in approximately 69,000 autopsies, an incidence of one in 858. However, as far as we were able to ascertain, the case here presented is the first reported case of a hypernephroma occurring in such a kidney.

The case, aside from being unique, has several other unusual features, both from the clinical and pathological aspects.

CASE REPORT*

E. J., white, aged 60, a widow, was admitted to the hospital December 2, 1925, complaining of polyphagia, occasional polydipsia, increasing weakness, pruritus vulvae, nocturia, chilliness, insomnia and pains in the first two toes of the right foot. A sister had diabetes. The patient had had three normal pregnancies and one miscarriage. Menopause occurred at 50. She had been under dietetic treatment for diabetes mellitus for several years and two years previously the distal portion of her right fifth toe had been amputated for gangrene. Five years ago she weighed 175 pounds, while at present her weight was 106¾ pounds. Her physical examination disclosed evidence of emaciation, generalized arteriosclerosis, a firm globular enlargement of the thyroid and a dry gangrene of the distal portion of the right second toe. The urine was negative for sugar, acetone and diacetic acid and on microscopical examination showed an occasional hyaline cast. She had a slight anemia and her blood chemistry gave the following figures: Sugar 295 mg., CO_2 71, Urea N. 16.6 mg., Creatinine 0.6 mg., Uric Acid 3.0 mg. Her temperature on admission was 99° F. and her basal metabolism +39%.

Commencing with a diet composed of protein 32 gms., fat 96 gms. and carbohydrate 30 gms., the amounts were gradually raised to protein 50 gms., fat 200 gms. and carbohydrate 70 gms., at which point sugar was found in the urine. In conjunction with increasing doses of insulin up to 15 units twice a day, her diet was then raised

*From the service of Dr. DeWitt Stetten.

to protein 100 gms., fat 200 gms. and carbohydrate 100 gms. without the appearance of sugar in the urine.

On January 11th, her blood sugar was 168 mg. and her CO_2 63.3. On the 13th, the carbohydrate was increased to 130 gms. About this time, however, she began to do poorly. Her blood sugar was 250 mg. on the 28th and the gangrene, which had remained more or less stationary, slowly extended, so that by February 22nd it had involved the lateral surfaces of the foot and all the toes except the third. Sugar appeared in the urine February 14th and slowly mounted to 3.3% by February 23rd. Her temperature fluctuated between 99°F. and 101°F. On March 1st, the leg was amputated below the knee. She suddenly became worse on March 3rd and a blood chemistry on that day showed sugar 400 mg. and CO_2 52.8. The urine contained 0.5% sugar and was positive for acetone and diacetic acid. In spite of large doses of insulin, hyperdermoclyses and colon irrigations with sodium bicarbonate, she lapsed into coma, and on the 5th her blood sugar was 660 mg. and her CO_2 19.5. By the evening of the 6th, the blood sugar had been forced down to 74 mg. while her CO_2 had risen to 48.5. Pulmonary oedema developed and death followed.

AUTOPSY FINDINGS

The body was that of a well developed, elderly female, showing signs of marked emaciation. The eyeballs were rather prominent and there was a globular, cystic enlargement of the right lobe of the thyroid, the size of a small tangerine. The right leg below the knee was missing, the stump showing a clean, recent, unsutured, operative wound. Both upper lobes of the lungs showed senile emphysema, with oedema and a patchy pneumonia of the lower lobes. The heart weighed 450 grams, and showed hypertrophy of the musculature. The cusps of the mitral valve were somewhat shortened in width and their free edges were markedly thickened. The aorta contained many raised, firm, yellowish plaques scattered diffusely throughout its entire length. The gastric mucosa was congested. The intestines were apparently normal. The uterus and adnexae were atrophic. The spleen weighed 300 grams, and was densely adherent to the surrounding structures. It was rather soft and its cut surface was pale red in color and the pulp easily scraped off. The markings were not prominent. The liver was moderately enlarged, weighing 2100 grams. The capsule was smooth and glistening. On section, it had a mottled appearance, the centers of the enlarged acini being reddish brown and the periphery yellowish in color. The pancreas was somewhat reduced in size, its surface was irregularly nodular and its consistency markedly increased. The adrenals were enlarged, especially the left, which was about twice the normal size. The latter contained a yellowish nodule, about the size of a

grape, in its cortex. The kidneys were dystopic and joined together by their lower poles at the level of the promontory of the sacrum, in front of the great vessels. They converged slightly downward and inward and differed markedly in size. The left measured 16 cm. in length x 5.5 cm. in width x 3.5 cm. in thickness, while the right measured only 10 cm. in length x 5 cm. in width x 2.5 cm. in thickness. Their anterior surfaces showed the fetal lobulations, while the posterior surfaces were smooth. Situated in the bend of the horseshoe was a large circumscribed, globular tumor mass, 8 cm. x 3.5 cm. It was surrounded by kidney tissue laterally and above. The pelves were single, discrete and rotated anteriorly. The right

Fig. 1. Hypernephroma in Bend of Horseshoe Kidney. (Posterior View.)

pelvis was enlarged, flattened out and markedly irregular in shape. The right ureter coursed over and was adherent to the anterior surface of the tumor. On section, the tumor presented a large central area composed of glistening, firm, grayish white tissue, containing many small butter-yellow islands. Around the periphery were several similar, though larger islands, some of which exhibited areas of softening and hemorrhage. (See Fig. 1.)

MICROSCOPICAL EXAMINATION

The lungs showed marked tortuosity and congestion of blood vessels, oedema and small areas of bronchopneumonia in the lower

lobes. The heart showed a hyaline degeneration of the muscle fibres and a slight interstitial fibrosis. The spleen was congested and showed an increase in the pulp cells and a slight fibrosis of the reticulum and trabeculae. There was a diffuse parenchymatous degeneration and slight fatty infiltration of the liver cells. There was a marked overgrowth of the interstitial fibrous tissue and atrophy of the parenchyma of the pancreas. The number of islands of Langerhans was diminished and scattered throughout the acinous tissue were small fibrous nodules, probably replaced islands. The adrenal cortex contained a very vascular adenoma, composed of typical adrenal cells, rich in lipoid. A small septic infarct was also present in the cortex. It was irregular in shape and consisted of a central area of cortical tissue in all stages of necrosis and disintegration and a peripheral zone of pus cells. A few lymphocytes and mononuclear cells were seen. (Figs 2. and 3.)

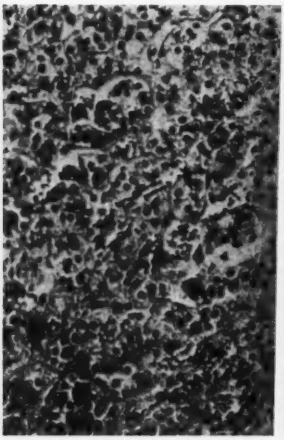

Fig. 2—X 250 Adenoma of Left Adrenal.

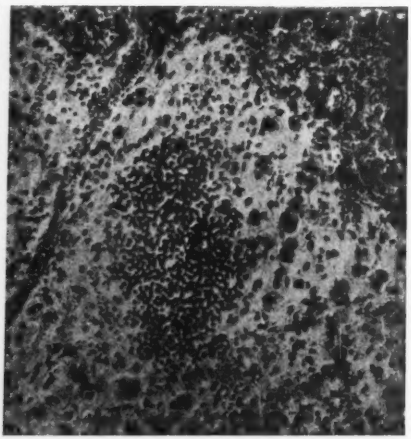

Fig. 3—X 250 Septic Infarct of Left Adrenal.

Sections through the tumor revealed collections of large, foamy, partly transparent, polygonal, plant-like cells, arranged either in small circular groups or as cords or sheets of cells separated and supported by a small amount of fine, extremely vascular connective tissue. In one area, the cells enclosed lumina-like spaces and had a papillary structure. The tumor cells showed marked hydropic degeneration and extensive necrosis. Small hemorrhages were frequent and in the necrotic area were several cystic spaces filled with blood. A large venous thrombus was seen containing an unusual number

of polymorphonuclear leucocytes. There was a slight round celled infiltration in a few localized areas.

Anatomical Diagnosis: Cystic goiter; Senile emphysema; Bronchopneumonia; Myocardial degeneration; Chronic endocarditis of mitral valve; Hypertrophy of both ventricles and dilatation of the right; Athero-sclerosis; Acute splenic tumor; Parenchymatous degeneration liver; Chronic interstitial pancreatitis; Adenoma and septic infarct of adrenal; Hypernephroma in horseshoe kidney; Amputated right leg.

COMMENT

As far as we were able to discover, only two cases of tumor in a horseshoe kidney are reported in the literature. Both, however, were sarcomas, limited to the right kidney, and affected very young children. The first, mentioned by Hildebrand[3] in 1894, was more fully reported by König and Pels-Leusden[4] in 1900, and the second was published by Gibbon[5] in 1909.

Besides the unusual type of tumor present in our case of horseshoe kidney, its situation in the bend of the horseshoe is also of interest.

Since Blum[6] in 1901 discovered that the subcutaneous injection of adrenal extract produced glycosuria, numerous workers have studied the relationship of epinephrin to carbohydrate metabolism. Metzger[7] proved that the glycosuria was due to an increase in sugar in the blood, and Vosburgh and Richards[8] and Iwaroff[9] showed that the overproduction of glucose depended upon an accelerated breaking down of glycogen in the body. Macleod and Pearce[10] found that the injection of epinephrin into portal circulation of living animals was followed by an increased glycogenolysis in the liver, while Ringer[11] after making animals glycogen-free by a combination of hunger, cold and phloridzin, found no change in the elimination of sugar or in the D:N ratio. Cannon and his co-workers[12], using the denervated heart as an indicator, have clearly demonstrated the antagonism between the glycogenolytic action of the medulli-adrenal secretion and the glycogenetic action of insulin in the maintenance of the glycemic equilibrium.

In our case, the presence of a septic infarct in the adrenal with consequent irritation and over-secretion of epinephrin may well explain the sudden increase in the severity of the diabetes in spite of a restricted diet and fairly large doses of insulin.

The day before the patient's death, although practically on a starvation diet, her blood sugar rose to 660 mg. The source of this high blood sugar level is easily understandable on the basis of an increased glycogenolysis incident to an hyperadrenalinemia.

The origin of the infarct was, in all probability, the thrombosed vessels in the gangrenous toes. In fact, the turning point in the progress of her illness was coincident with a pronounced extension of the gangrene to the foot.

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HYPOTHYROIDISM AS A COMPLICATION OF DIABETES MELLITUS

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Hypothyroidism as a complication of juvenile diabetes deserves special comment. Marked hypothyroidism was recognized three years ago in a diabetic girl of fifteen years, on her return to my office for routine supervision two months after she had left the sanitarium. Her metabolic rate at that time was minus 38%. Her record during the first month of insulin therapy was reported (1) because of a severe lipemia and lipemic retinalis. No discussion of her hypothyroidism, however, was given. During these three years, it has been necessary to continue thyroid therapy which has been controlled by metabolic rate determinations.

During the last three years, hypothyroidism has also been observed in several other diabetic children and young adults. Thus the realization of such a possible complication, especially in the young diabetics, seems important to keep in mind. The presence of physical and mental sluggishness, dry skin and hair, slow pulse, and in some cases a gain in weight, should suggest the possibility of hypothyroidism.

A study of a series of young diabetics from the point of view of possible hypothyroidism is in progress. This report includes metabolic rate determinations and a discussion of the symptomatology and treatment of the patients with hypothyroidism.

It is realized that the metabolic rate is diminished with under-nutrition. Our cases, however, are all receiving sufficient calories, and the diabetic condition in each patient is controlled satisfactorily with insulin.

This preliminary report is given at this time because of the absence in the literature of any emphasis on hypothyroidism as a complication in the young diabetic.

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Book Review

DIE KASTRATION BEI WIRBELTIEREN UND DIE FRAGE VON DEN SEXUALHORMONEN. Knud Sand, in Handbuch der Normalen und Pathologischen Physiologie, Berlin, 1926. Julius Springer.

This section of the Handbuch comprises the following articles by Dr. Sand:

1. Die Kastration bei Wirbeltieren und die Frage von den Sexualhormonen.

2. Transplantation der Keimdrüsen bei Wirbeltieren.

3. Der Hermaphroditismus bei Wirbeltieren in experimenteller Beleuchtung.

4. Die Keimdrüsen und das experimentelle Restitutionsproblem bei Wirbeltieren.

Sand presents an excellent, well illustrated summary of the evidence on each of the topics treated.

Abstract Department

Microspirometric researches on hormones (Mikrorespirometriscke Untersuchungen über die Hormonwirkungen). I. Insulin. Ahlgren (G.), Skandin. Arch. f. Physiol. (Leipz.), 1926, **47**, 271-280.

Using a microspirometer, Ahlgren found in eight experiments that O_2 consumption and Co_2 production by minced frog muscle was augmented by adrenalin in concentrations of 1:10,000,000 to 1:100,000,000,000. More concentrated solutions depressed the gas metabolism.—R. G. H.

The effects of epinephrin on the response of the frog heart to stimulation of the accelerator nerve. Barlow (O. W.) & Sollmann (T.)., J. Pharmacol. & Exper. Therap. (Balt.), 1926, **28**, 157-158.

During acceleration produced by perfusion of the frog heart with solutions, diminution of response from stimulation of the accelerator nerve was closely proportional to the degree of epinephrin augmentation, even after depression of the cardiac musculature has reduced the amplitude. Augmentation by the heart perfused with Ringer solution occurs in about the same degree from both epinephrin and from stimulation of the accelerator.—C. I. R.

The role of the suprarenal gland in the natural resistance of the rat to diphtheria toxin. Belding (D. L.) & Wyman (L. C.), Am. J. Physiol. (Balt.), 1926, **78**, 50-55.

It is known that double suprarenalectomy increases the sensitiveness of rats to a variety of poisonous drugs and toxins, and that rats have a high natural resistance to diphtheria toxin. Both suprarenal glands were removed from albino rats in one operation and the control rats received the same operative procedure except the removal of the glands. The highest post-operative mortality in the suprarenalectomized animals occurred with fluctuations in room temperature and rectal measurements indicated a lessened ability of the suprarenalectomized rats as compared with the controls to maintain their body temperature in a cold atmosphere. An approximation of the lethal dose of diphtheria toxin administered intraperitoneally two to three weeks after operation showed that the controls were about two and one-half times as resistant to the toxin as the suprarenalectomized rats. The amount of diphtheria toxin in the blood four hours after an intraperitoneal injection of one M.L.D. per gram of body weight was measured by the Roemer

intradermal method in guinea pigs. The suprarenalectomized rats had approximately 2.75 times as much free toxin in their blood as the control rats. Suprarenal deficiency apparently renders less effective the normal mechanism of the rat for the elimination or destruction of diphtheria toxin.—D. L. Belding.

Spurious hermaphrodism of suprarenal origin (Zur Kentniss der suprarenalen Pseudarrhenie). Feldmann (E.), Arch. f. path. Anat. u. Physiol. (Berl.), 1926, **259**, 608-616.

The case of a child, 7 years old, with well proportioned male external genitalia and only female internal sex glands is described. There was an accompanying enlargement of the adrenal glands involving only the cortex. In fact, the medulla seemed hypoplastic. The author holds that this hyperplasia of the adrenal cortex was probably present from very early embryonic life and was the causative factor in the production of the disturbed development of the sexual organs.—W. J. A.

Carcinoma of cortex of suprarenal gland with virilism. Feinblatt (H. M.), Arch. Int. Med. (Chicago), 1926, **38**, 469-473.

A young woman progressively developed virile characteristics, including facial hypertrichosis, the masculine type of abdominal and axiliary hair, a low pitched voice and a masculinoir facies. Later, a tumor was palpated in the region of the right kidney. Necropsy revealed a large carcinoma of the cortex of the right suprarenal gland with extension by way of the vena cava, but without distant metastasis.—Author's Summary.

The maximum metabolism and the suprarenal capsules. Giaja (J.) & Chabovitch (X.), Compt. rend. Acad. d. sc. (Par.), 1925, **181**, 885-886.

The authors have shown in three rat experiments certain modifications in thermogenesis resulting from the removal of the adrenals: 1, decapsulated rats are unable to accommodate their thermogenesis; 2, maximum metabolism is lowered to a point confusing it with basal metabolism; 3, injection of .4 mgs. of adrenalin increases the respiratory quotient; the normal maximum of metabolism, however, is never reached. From these facts they conclude that the adrenal capsules play an important role in thermogenesis.
—C. M. MacFall.

The effect of nephrectomy and suprarenalectomy in the rat on resistance. Gottesman (Jessie M.) & Gottesman (J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 45-48.

The authors summarize as follows: "It has been shown that the duration of life of nephrectomized rats is not affected by injec-

tions of the same typhoid vaccine which regularly shortens the life of suprarenalectomized rats. It has also been shown that suprarenalectomized rats have a refractory period of approximately four days before any marked drop in resistance is manifest. These findings, together with the fact that the suprarenalectomized animals fully retain their ability to form anti-bodies and to regenerate the thymus and lymph tissues, suggest that suprarenalectomy exerts a specific physiologic influence on resistance."—J. C. D.

The influence of burns on epinephrin secretion. Hartman (F. A.), Rose (W. J.) & Smith (E. P.), Am. J. Physiol. (Balt.), 1926, **78**, 47-49.

Experiments on anesthetized cats show that burns cause an increase in the epinephrin output (dilatation of completely denervated iris). The increased output sometimes persists for a few hours. There was depletion of epinephrin and of lipoids in the adrenals of these animals. Therefore, burns cause an excessive activity of the adrenals.—Author's Summary.

The effects of bilateral suprarenalectomy on the life of rats. Jaffe (H. L.), Am. J. Physiol. (Balt.), 1926, **78**, 453-461.

Ninety rats were followed for a period of 1 year after suprarenalectomy and upon analysis were divided into 3 groups. The first group, 35%, died within 30 days after operation from acute and subacute insufficiency, a great majority of deaths occurring before the 13th day. The second group, comprising 46% of the total, consisted of animals which survived suprarenalectomy for many months, but which were chronically insufficient and suffered from progressive emaciation resulting in marked or complete absence of fat, asthenia, and lowered resistance leading in some instances to snuffles and skin infections. Most of these animals died within 7 months after operation, no gross accessories being found at autopsy. The syndrome of chronic suprarenal insufficiency in rats has never been adequately emphasized. The third group, 19% of the entire series, consists of animals in which suprarenalectomy is followed by no demonstrable clinical effects. These animals are biologically normal rats in every respect, and large accessory cortical masses are always found at autopsy. When rats are studied clinically for many months after suprarenalectomy, the seriousness of this operation in regard to the ultimate life of the animal becomes evident. Contrary to the reports in the literature, we found that fully 80% of rats die from the effects of suprarenal removal within a year after operation.—Author's Abstract.

Central stimulation of the adrenals and the paraganglia during insulin intoxication (Ueber die zentrale Reizung der Nebennieren und der Paraganglien während der Insulinvergiftung). Kahn (R. H.), Arch. f. d. ges. Physiol. (Berl.), 1926, **212**, 54-63.

The results of H. Poll, indicating that after insulin intoxication in the mouse morphological changes are found in both portions of the adrenals, are confirmed for the rabbit and for the dog. In the dog the changes are also apparent in the abdominal chromaphil body. The chromaphil tissue so changed shows a diminution of its adrenine content. In rabbits the toxic action of insulin on the adrenal medulla takes place through nerve channels, since sectioning of the splanchnic protects the adrenal from these changes. Hence it would appear that insulin acts through the central nervous system on the paraganglia, comparably to the actions following sugar-puncture, asphyxia, etc. The morphological changes recorded are diminution of the size of cells, formation of vacuoles, lessening of the color-staining reactions, and disappearance of granules.

—A. T. C.

Rôle of suprarenals in blood sulphur regulation. Loeper et al., Presse méd. (Par.), 1926, **34**, 1209-1211; Abst. J. Am. M. Ass., **87**, 1689-1690.

The authors noted an increase of blood sulphur in three cases of Addison's disease; the proportion of the oxidized sulphur was reduced, while that of the neutral sulphur was increased. Analogous phenomena were observed in dogs after removal of a suprarenal. Further experiments showed that the blood of the suprarenal artery contains much more sulphur than that of the corresponding vein and that in the artery the proportion of oxidized to neutral sulphur is lower than in the vein. It appears evident that the suprarenal glands retain a part of the blood sulphur, especially of the neutral. This was confirmed on large numbers of the suprarenal glands of sheep. A part of this sulphur is utilized for formation of the suprarenal pigment. Melanoderma, they hold, is the consequence of an exaggerated elimination by the skin of the sulphur retained in excess in the blood, in conditions in which suprarenal function is impaired.

Antagonism of barium chloride and glandular extracts on chromatophores by epinephrin and ephedrine. Nadler (J. E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 53-54.

In the squid epinephrin antagonizes extracts of the parathyroid and of the anterior and posterior lobes of the hypophysis more intensely than ephedrine. The latter is more effective in antagonizing barium chloride.—J. C. D.

The effect of epinephrin and prolonged accelerator stimulation on the response of the frog heart to stimulation of the cardiac-inhibitor nerve. Sollmann (T.) & Barlow (O. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, **28**, 159-164.

Response of the frog heart to stimulation of the vagus is increased by perfusion with epinephrin and by continuous stimulation of the accelerator nerves, and the inhibitory response becomes progressively greater the longer the perfusion or accelerator stimulation are continued and recovery after discontinuance of these procedures is quite slow. The authors suggest that these results are due to accumulation of muscular metabolites.—C. I. R.

The effects of fatigue and temperature on the adrenal bodies of the rat. Vincent (S.), Quart. J. Exper. Physiol. (Lond.), 1925, **15**, 319-326.

White rats, exercised at a room temperature of about 14.5° C., exhibit a fall of body temperature and a marked reduction of the chromaphil reaction of the adrenal medulla. Exercise at 18-20° C. results in no change in body temperature, but above 20° C. there is an increase in body temperature. Under these conditions there is no change in the chromaphil reaction. The author concludes that any effect of exercise upon the chromaphil reaction is secondary to the lowering of body temperature.—P. M. Harmon.

The influence of organ extracts and especially of extract of corpus luteum on the blood-coagulation time (Der Einfluss von Organextrakten im besonderen von Corpus-luteum-Extrakten auf die Blutgerinnungszeit). Alzinger (F.), Arch. f. d. ges. Physiol. (Berl.), 1926, **213**, 548-555.

Organ extracts were made by boiling 20 minutes with water or with alcohol or ether, cooling and filtering. Sodium chloride was added to the first to 0.85%, while the latter was evaporated to dryness and the residue dissolved in 0.85% sodium chloride solution. Such extracts of corpus luteum, liver, spleen, or ovary produced definite effects on the coagulation time, aqueous extracts slowing and alcoholic and ether extracts hastening it. The accelerating compounds are soluble in alcohol and ether and thermostable. The difference of effect is more marked the lower the temperature.

—A. T. C.

The heart regulating hormone of the liver and other pharmacological effects of the same (Das Herzregulierende Hormon der Leber und die Aenderung Pharmakologischer Wirkungen Durch Dasselbe). Asher (L.), Schweiz. Med. Wchnschr. (Berl.), 1926, **56**, 921.

Asher states that he has been able to isolate a hormone from

the liver which increases the strength of the heart beat, increases the heart rate, and diminishes the vagus irritability. This substance may be described as an agent which assists sympathetic action. Liver extracts were prepared from liver powder. The exact nature of the process is not stated. The liver extract produced a slowing of the pulse and elevation of blood pressure. Tests for the presence of bile salts were negative. The liver hormone which has been obtained by perfusion of liver has a different action from that of liver extract. Experiments with sodium cholate show an action similar to that of the liver hormone, and Asher believes that they are probably identical. Asher emphasizes that the cholate is nitrogen free, and is therefore a hormone which does not belong to the group of amines to which so many other hormones belong.

—R. H. Major.

Further observations on patients with hypertension and increased basal metabolic rate. Boas (E. P.) & Shapiro (S), American Heart Journal (St. Louis), 1926, **1**, 643.

A group of patients is described in which are presented the following clinical characteristcs: hypertension (systolic and diastolic), increased basal metabolic rate, tachycardia, nervousness, loss in weight, and pigmentation of the skin. It is believed that these symptoms constitute a special syndrome which should be distinguished from both exophthalmic goiter and uncomplicated hypertension. Including those mentioned in a previous communication, ten such cases are described by the authors.—Author's Abst.

Endocrine glands in allergy. Duke (W. W.), in Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy. The C. V. Mosby Co. (St. Louis), 1925, 145-146.

The organs of internal secretion evidently play a marked role in the symptomatology of reactions of hypersensitiveness (allergy). This should seem self-evident when we bear in mind that the great majority of cases, regardless of their severity, can be completely relieved through the action of adrenalin. Many cases relieved by pituitary extract. If adrenalin has a normal physiologic antagonist, and one might easily believe that this is the case, an overproduction in this might, on theoretical grounds, give rise to a reaction. Thyroid extract in occasional cases is beneficial especially in patients whose metabolism is below par and whose temperature runs markedly subnormal. The above influences from a practical viewpoint are effective in many cases, but would seem usually to be secondary factors in the etiology of reaction.—R. G. H.

Endocrine glands of rabbits fed cod liver oil or irradiated cholesterol. Gates (F. L.) & Grant (J. H. B.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 59-62.

Neither treatment appreciably influenced the weights of the ductless glands.—J. C. D.

A study of jaw and arch development considered with the normal and abnormal skeleton. Howard (C. C.), The International Journal of Orthodonia, Oral Surgery and Radiography (St. Louis), 1926, **12**, 3-16.

Howard's studies indicate that conditions met by the orthodontist are frequently associated with other anomalies that render evident their endocrine etiology. Adequate treatment often necessitates consideration of this etiology, local measures being of merely temporary benefit. On an examination of over six hundred cases in the Good Samaritan Endocrine Clinic, forty-one obese subjects of posterior lobe pituitary deficiency were found. All had normal arch and jaw development, with almost perfect teeth. Nineteen cases of hypothyroidism or Mongolian idiocy were seen. All showed congenital absence of teeth—from one to twelve each.—R. G. H.

Studies on the conditions of activity in endocrine glands. XVIII. Locus of the calorigenic action of adrenalin with observations on tissue metabolism. Hunt (H. B.) & Bright (Elizabeth M.), Am. J. Physiol. (Balt.), 1926, **77**, 353-369.

Amytal anesthesia increases the resting metabolism of the cat about 10%. The basal rate of metabolism in muscle is low, 0.50 to 1.0 calorie per kilo per hour. In the liver it is high, 10 to 20 calories per kilo per hour. In the other viscera it averages 2 to 3 calories per kilo per hour. Adrenalin given in a dosage of 0.005 mgm. per kilo per minute for six minutes, produces rises in total metabolism which averages 10.6% during the following 20-minute period. The peaks of the rises average 19.0%. The increased metabolism of the heart would account for only one-third of this total rise. Adrenalin has a general calorigenic action on tissue metabolism.—Author's Summary.

The basal metabolic rate in cases of chronic cardiac disease and in cases of hypertension. Shapiro (S.), Arch. Int. Med. (Chicago), 1926, **38**, 385.

The metabolic rates determined under strictly basal conditions were studied in a series of forty-two cases of heart disease, including twenty-two patients with valvular lesions, fifteen with hypertension and cardiac hypertrophy, two with congenital heart disease and three with functional tachycardias. In three cases the basal metabolic rate was found to be definitely elevated above normal. These three patients had dyspnea or hyperpnea. In the remaining thirty-nine cases of heart disease unaccompanied by dyspnea at rest the basal metabolic rates were within the accepted normal limits. The

author concludes, therefore, that the basal metabolic rate in patients with organic heart disease is normal. High readings are usually due to dyspnea. The cardiac overactivity which occurs in a heart compensating for an organic heart defect or maintaining an elevated vascular tension does not detectably elevate the heat production.—Author's Abst.

The calcium content of the blood. Waldorp (C. P.), Prensa méd. argentina (Buenos Aires), 1926, **13**, 140; Abst. J. Am. Ass., 1926, **87**, 1163.

Waldorp's extensive study of the calcium content of the blood confirms the influence of the nervous system on the fluctuations. The subject should be kept quiet before testing the blood calcium with intravenous injection of a given quantity of calcium. The resulting hypercalcemia lasts in normal conditions for an hour and then the calcium returns to the former level. In 26 cases of thyroid disease with high basal metabolism, the blood calcium content was low; in 9 of 18 cases the sugar content was abnormally high. The calcium content kept persistently low in a case of hypothyroidism and in 3 cases of exophthalmic goiter under thyroid treatment. The calcium content was below normal also in 4 cases of acromegaly and in one of a pituitary tumor. The calcemia in the latter case fluctuated with the increased or decreased functioning of the anterior lobe of the pituitary. In 3 cases of eunuchoidism the basal metabolism was high in 1, with low calcemia, but in the 2 others both were within normal range. His research on the parathyroids confirms their fundamental roles in the maintenance of normal calcemia.

The relation between corpus luteum and the mammary gland. Drummond-Robinson (G.) & Asdell (S. A.), J. Physiol. (Lond.), 1926, **61**, 608-614.

The investigation failed to throw any light on the question whether mammary development may occur in the absence of the corpus luteum if the foetus is present, since abortion always followed the removal of the corpus luteum. Clean-cut evidence, however, was obtained as to the relation between corpus luteum and mammary growth and function. In this work virgin goats were used, care being taken to select animals which had not been bred for high milk production. The sire was the same in all cases. The removal of the corpus luteum was timed with reference to the appearance of abundant globulin secretion and the beginning of mammary proliferation, which events occur both in goats and in cows at about the middle of gestation. Some of the operations were performed well before this time and some after it. When performed before the globulin stage of the gland was reached milk was not

secreted. Removal of the corpus luteum after the globulin stage was reached was followed by an immediate copious secretion of milk. After the stimulus for growth has been given by the corpus luteum the mammary cells seem able to attain the globulin stage without further continued stimulation, but if the stimulus is removed by excision of corpora lutea the attainment of the globulin stage is not followed by milk secretion. The postulation of an inhibitory hormone to account for the usual decline of milk secretion in late pregnancy is unnecessary since it seems unlikely that cells stimulated to growth and division by the corpus luteum at the half-way stage of pregnancy can continue to secrete.

—E. P. Durrant.

A study of the effects of testicular extract upon the pregnant guinea-pig and the fetus. Emery (F. E.), Tr. Am. Micr. Soc. (Buffalo), **45**, 44-53.

Virgin female guinea-pigs and females that were kept with males were injected intraperitoneally for a period of six months with saline extracts made from desiccated testicular substances. The general systemic reactions in the injected animals were evidence of pain at the area where the injections were made, watering of the eyes and occasionally coma, but rarely death. Chronic peritonitis developed in most of the animals. Histological examinations of the ovaries of the injected animals showed marked degenerative changes with atrophy of the Graafian follicles and a tendency to cystic formation. This condition was more marked the younger the animal at the beginning of injection. The young born from injected mothers were apparently normal with regard to weight, the ratio between males and females, and fertility. Histological examinations of the gonads of the young born from treated mothers showed the testes were normal, but the ovaries were shrunken and there seemed to be more atresia of the Graafian follicles than in normal animals. The power of reproduction in the females that were injected seemed to be more closely correlated with the degeneration produced in the ovaries than with the general emaciation, because the animals, in many instances, did not breed for considerable periods after they had apparently recovered their normal weight. In control animals injected with ovarian extract and amniotic fluid degenerative changes in the ovary were not so marked and cystic formation was rare.—Author's Summary.

Female sex hormone. Frank (R. T.) & Goldberger (M. A.), J. Am. M. Ass. (Chicago), 1926, **86**, 1686-1687; Abst. A. M. A.

Frank and Goldberger have obtained the female sex hormone from blood specimens by means of lipoid extraction performed under

identical conditions by identical methods. The results are sufficiently concordant to be considered quantitative. Blood has been obtained from 38 patients. In some instances, specimens have been taken at intervals of from 5 to 7 days through two monthly cycles from the same patient. From this investigation it has become evident that: 1. The amount of female sex hormone found in the circulating blood of the human female varies during the menstrual cycle. An abrupt increase takes place beginning between the tenth to the fifteenth day counted from the first day of the last menstruation. 2. The female sex hormone is present in greatest concentration in the circulating blood near the first day of menstruation. 3. With the onset of menstruation, the female sex hormone abruptly diminishes in the general circulation. 4. The female sex hormone appears in the menstrual blood, there being present in from triple to six fold the concentration found in the circulating blood. 5. In certain types of menorrhagia and metrorrhagia, the female sex hormone many be (a) absent from both the circulating and the uterine blood; (b) in others, present in both the circulating and the uterine blood. 6. In certain amenorrheas, an increase in amount of the female sex hormone may be demonstrated in the circulating blood. From these observations, the authors feel justified in concluding that: (a) The female sex hormone secreted by the maturing follicle reaches the general circulation. (b) The sudden increase of female sex hormone found from 10 to 15 days after the last menstruation may be used approximately to determine the time of ovulation. (c) The female sex hormone secreted by the corpus luteum likewise reaches the general circulation, continuing the pregravid stimulation of the genital tract and breasts as demonstrated by other methods in a previous communication. (d) During the pregravid stage, either (1) a concentration and storage of the female sex hormone takes place in the uterine tissues, or (2) the uterine mucosa at the time of the menses filters out the female sex hormone from the circulating blood. (e) Two types of menorrhagia or metrorrhagia occur, the one with oversecretion, the other with undersecretion of the female sex hormone. Further study may enable us to elaborate proper forms of treatment based on the etiology. (f) Some amenorrheas may be due to persistence of the corpus luteum, as evidenced by a persistence and undue concentration of the female sex hormone in the circulating blood.

X-ray treatment of hypofunction of the ovary, with special reference to the regulation of menstrual function. Hirsch (I. S.), Radiology, 1926, **7**, 93.

The method of treatment has been called the stimulative treatment of the ovary. In certain cases, menstruation—irregular in interval, duration and amount, occasionally scanty and occasionally

profuse—cannot be ascribed either hypo or hyper, but to a dys or a disordered function, in which X-ray treatment acts as a regulator. The form of ovarian hypofunction suitable for this therapy may manifest itself as an amenorrhea, oligo-, opso- or a combined form and as an associated sterility. In all the types of cases suitable for treatment, there must be direct or indirect evidence that ovarian tissue exists in sufficient amounts to respond to the action of radiation. The numerous forms of treatment for the menstrual disturbance resulting from the insufficiency of ovarian function have all of them been of so little permanent value that there is justification in stating that there is no medicinal therapy which is definitely able to influence ovarian function. This applies to medication, physical measures, hydro or thermotherapy, active and passive gymnastics, massage, etc. The connection of the endocrine glands with the function of the genital apparatus has been recognized in recent years as quite definite for the ovaries, the thyroid, the pituitary, and the adrenal glands. Consequently, the administration of glandular extracts, either single or in combination (for instance, of entire ovary or liquor folliculi, corpus luteum, thyroid, the anterior and posterior lobes of the pituitary gland), has become quite customary in gynecological therapeutics. The results have been, however, neither striking nor permanent. The X-ray treatment consists in the administration of a small dose of radiation to each ovary. The dose necessary to produce the desired effect is 15 per cent of the castration dose delivered to each ovary through four portals. It is necessary to treat both sides because of the alternate ovulation. The four portals which take in all the pelvic structure may be irradiated at one sitting, or a portal at a time with intervals of a day or two. The series should not be repeated until after a lapse of several months. A slight variation from the 15 per cent may be necessary, depending (1) on the age, (2) thickness of abdominal wall, (3) duration of ovarian hypofunction. There should be no irradiation sickness, and no change in the skin of the portals treated. This treatment is contra-indicated in symptomatic amenorrhea, associated with such general systemic diseases as lues, tuberculosis, nephritis, pernicious anemia, also when secondary to adnexal disease, tumors or cystic disease of the ovary. Amenorrhea in advanced age or of very long duration, or that resulting from curettages after numerous abortions, does not respond to this treatment. In dystrophy-adiposo-genitalis, the involvement of other endocrines may necessitate other treatment. Thirty-six cases were studied. The result showed that in twenty-two of the cases treated, menstruation appeared after the treatment and in the majority of cases followed during the entire period of observation, and that the somatic and physical symptoms of the ovarian hypofunction disappeared rapidly after menstruation set in.

The longest period of amenorrhea to be followed by a menstruation after the irradiation was six years. Successful results were obtained in a woman of 30 years who had not menstruated for three years, in a woman of 28 who had not menstruated for two years, and in a woman of 34 years who had not menstruated for seventeen months. The interval between the first radiation and the menstruation varied, but in the majority of cases it was about twenty-eight days. In two cases the duration was two and three weeks, respectively. In some of these cases, simultaneously with the regulation of menstruation, dysmenorrheal symptoms were favorably influenced. In other cases there was no improvement of menstrual function. In some cases the pain with the first menstruation was very severe. In some cases of oligomenorrhea the Increase of the menstrual function was abnormal. In certain cases of hypomenorrhea, in which there was a marked adiposity with the menstrual disturbance, the adiposity was reduced after the onset of menstruation, without any other therapeutic measure. One of these cases lost thirteen pounds after the treatment, one lost forty-seven pounds and one sixty pounds.

Besides this, there are seven cases treated for hypomenorrhea in which, following regular menstrual periods, pregnancy ensued. Out of five births there were four healthy children. The action of the radiation is to produce degeneration and retrogression of the graffian follicle whose secretory activity exercises an inhibitory effect in preventing further follicular rupture, ovulation and therefore menstruation. The results of this form of treatment lead to the conclusion that a certain dosage of radiation in carefully selected cases is capable of producing improvement in ovarian function, as shown by the regulation of menstruation and the induction of pregnancy, with the birth of healthy children. There cannot be any objection to this form of treatment on the ground that the already diminished ovarian activity can be still further diminished by the small doses of radiation. If the condition of the ovary is such that this should actually take place, nothing is lost, for such an ovary is hopelessly incompetent to produce the menstrual mechanism, or to produce an ovum capable of fecundation.

—Author's Abstract.

The effect of different ovarian constituents on the blood sugar content (Zur Frage der inneren Sekretion der Sexualdrüsen. VII. Mitteilung. Ueber die Einwirkung der varschiedenen Ovarialbestandteile auf den Blutzuckergehalt). Kylin (E.), Ztschr. f. d. ges. Exper. Med. (Berl.), 1926, **51**, 599-602.

Using chiefly ovaries of the cow, the author injected subcutaneously into dogs a watery extract of graafian follicles, corpora lutea and ovarian parenchyma. With the follicular extract a rise in blood sugar followed in all cases. With extract of corpus

luteum a fall in blood sugar resulted. No uniform results were obtained from parenchyma extract. This latter was not unexpected, since the ovarian residuum doubtless contained remnants of old corpora lutea and a number of small follicles which had not been removed. As Collip has shown, an insulin-like substance can be obtained from the most diverse organs of the body, and though its presence might be explained as a local storage from the Islands, yet it must be considered as possible that the corpus luteum might produce a substance with insulin-like effects. In the course of the researches described extracts made from the ovaries of a 28-year-old mare gave results exactly opposite those from cows of sexually functional age. As this age seems to be at least equal to the climacteric in the human species, experiments are planned to determine whether there is in the ovary an inner secretion peculiar to the post-climacteric ovary, with a view to possible light on the various pathologic manifestations associated with that epoch.

—E. P. Durrant.

Ovarian hormone and metabolism. Lacquer, E. et al., Deutsche med. Wchnschr. (Berl.), 1926, **52**, 1331; Abst. J. Am. M. Ass., 1926, **87**, 1425.

Lacquer, Hart and de Jongh observed an increased metabolism in castrated female rats after injections of ovarian hormone. The hormone is quite stable. The crude preparation in oil resists heating to 360° C.; the pure aqueous solution resists 170° C. It may be boiled in 26% potassium hydroxide or in 26% sulphuric acid. It is easily adsorbed—even by a filter paper. It resists pepsin and trypsin, but hardly acts by mouth—perhaps because of adsorption.

Studies on the oestrous cycle in the rat. III. The effect of low environmental temperatures. Lee (M. O.), Am. J. Physiol. (Balt.), 1926, **78**, 246-253.

A study of the length and character of the oestrual cycle was made in two groups of albino rats, one series (16) of which was kept under rather constant conditions of room temperature (22° C.), while the other (15) was kept out of doors during the three coldest months of the winter of 1924-25 (December, January and February). The series under room temperatures showed normal oestrous cycles of 4.8 days average length throughout the period. The experimental animals showed cycles of the same average length as the controls during a preliminary period under room temperatures, and also during a final period indoors after being outside. During the period of exposure to low temperatures these rats showed lengthened oestrous cycles (average 8.6 days). The length of the cycles varied roughly with the environmental temperature. These

results are interpreted as being due both to the direct effect of temperature on ovarian activity and to the lowered general metabolism of these rats, shown by lowered body temperature and lessened activity. It seems likely that in a state of nature the oestrual rhythm may vary considerably with the environmental temperature. The body temperature of the rats varied from 31° C. to 38° C., depending on the environmental temperatures.

—Author's Abstract.

Studies on the internal secretions of the ovary. I. The distribution in the ovary of the oestrus-producing hormone. Parkes (A. S.) & Bellerby (C. W.), J. Physiol. (Lond.), 1926, **61**, 562-575.

Extracts of various ovarian tissues from the cow, pig and horse were measured for activity in mouse units. In 5 of 8 cases residual tissue had a greater activity than the corresponding liquor folliculi, while in the remaining 3 cases the liquor folliculi had a greater weight for weight activity. There appears to be some correlation between the size of the follicles and the relative activity of liquor folliculi and residual tissues.—E. Allen.

Estrus in parabiosis. Pfeiffer (H.) & Zacherl (H.), Klin. Wchnschr. (Berl.), 1926, **5**, 1522; Abst. J. Am. M. Ass., **87**, 1598.

Pfeiffer and Zacherl made parabiosis experiments on rats. They found that the estrual cycles of two united females are independent. Even pregnancy and lactation of one partner does not influence the cycle in the other. Only in parabiosis of a female with a male did the estrus disappear.

Clinical tests of ovarian follicular hormone. Pratt (J. P.) & Allen (E), J. Am. M. Ass. (Chicago), 1926, **86**, 1964-1968; Abst. A. M. A.

The effects of injection of ovarian and placental extracts into monkeys, as noted by Pratt and Allen, were as follows: The ovarian follicular hormone starts the periodic growth processes in the female genital tract. In case ovulation occurs, the corpus luteum in woman, and perhaps in other primates, may continue this anabolic endocrine influence, which probably decreases as the next menses approach. Menstruation seems to be partly due to the temporary absence of this secretion after it has been acting for a certain time. But since ovulation followed by corpus luteum formation often does not occur, a specific secretion of the corpus luteum is not a necessary causal factor in the menstrual cycle. That the corpus luteum may possibly have a regulatory influence is not questioned. This substance or a very similar one is probably secreted by, or stored in, the placenta. Its continuous availability throughout the gestation period would account for the absence of menstruation dur-

ing pregnancy. Clinical tests on humans were also made. The ovarian follicular hormone injected into patients represented two kinds of preparations. Both were begun by extracting follicular fluid with lipoid solvents. One was watery emulsion, the other an oil solution of residues. The potency of these extracts was tested before their clinical use by injections into spayed rats. This material was injected subcutaneously in the deltoid region. Although there are many differences between the menstrual cycle of primates and the estrous cycle of other animals, there is one thing common to all, and that is the periodic growth and regression of the uterus in response to stimulation from the ovaries. In primates this regression is accompanied by the menstrual flow, in other mammals it is not. In order to test the action of the follicular hormone on the human cycle, suitable individuals have been selected from time to time. The following groups have been chosen: 1. Artificial menopause. 2. Natural menopause. 3. Primary amenorrhea. 4. Scanty menstruation. 5. Immaturity. The observations made in these cases are summarized as follows: Injections of ovarian follicular hormone into primates, monkeys and human beings, from which ovaries have been previously removed, produce growth in the uterus. Removal of the ovarian follicular hormone by oophorectomy or cessation of injections brings on menstruation in monkeys. Uterine growth and accompanying subjective symptoms similar to those previously experienced at time of menstruation have resulted from injections into patients whose ovaries have been previously removed. No bleeding approximating that of normal menstruation has as yet appeared in women. In one case of scanty and irregular menses in which the ovaries were still intact, a definite increase in flow and regularity has resulted from injection of the hormone.

Testicular fluid obtained after the method of N. P. Krawkow. Ssentyurin (B. S.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, **48**, 712-723; Abst. Chem. Absts., 1926, **20**, 3183.

Testicular fluid obtained by passing Ringer-Locke solution through isolated testicles of the ox and horse exerts an inhibiting effect on the retrogression of secondary sex characteristics in castrated fowl. The testicular fluid has the power to decolorize dyes of the rosaniline group and the rapidity of the decolorization runs parallel with the physiological activity of the testicular fluid.

Study of an early human ovum and the functional similarity of the ovarian and placental "hormones." Young (J.), Edin. M. J., 1926, **33** (Trans. Edinburgh Obstetrical Soc.), 113-125.

Subject matter covered by title.—J. C. D.

The functional relationship between the pituitary body and the tuber centers. Collin (R.), Ann. de méd. (Par.), 1925, **18**, 428; Abst. Arch. Neurol. & Psychiat., **16**, 495.

The connection between the hypophysis and the tuber cinereum is not only nervous—myelinated fibers running within the infundibulum—but also hormonic. Collins has shown that the colloid of the middle lobe of the hypophysis can also be demonstrated in the infundibulum and in the perivascular spaces of the tuber cinereum. He emphasizes that the vegetative centers of this region are under the regulating influence of the hypophysis hormone and do not act as independently as recent publications suggest. In his opinion the overestimation of these vegetative centers without taking into consideration their correlation with the hypophysis will prove as one-sided as was the former endocrinologic point of view.

Demonstration of hypophyseal secretion in human cerebrospinal fluid taken from the cisterna magna. Janossy (G.) & Horvath (B.), Orvosi hetil (Budapest), 1925, **69**, 1033; Abst. Am. J. Dis Child., 1926, **32**, 605.

Before this, only animal experimentation proved that the secretion of the posterior lobe of the hypophyseal gland is always present in the cerebrospinal fluid. The authors used virginal uteri of rats for their experiments, and cerebrospinal fluid taken by cisterna or lumbar puncture. They found that the contraction of the uterus was always much stronger with cerebrospinal fluid of the cisterna puncture than that of the lumbar puncture. Their conclusion is that the secretion of the posterior lobe of the hypophysis reaches the cerebrospinal fluid through the infundibulum, and is diluted and partly reabsorbed in the subarachnoidal space.

The rôle of the hypophysis in infantile dystrophies. Lereboullet (P.), Ann. de méd. (Par.), 1925, **18**, 452; Abst. Am. J. Dis. Child., 1926, **32**, 600.

This is a critical review of recent literature. The so-called hypophysis syndromes in children are often produced by lesions of hypothalmic nuclei. Only gigantism and acromegaly may now be considered as pituitary diseases.

The anti-diuretic action of pituitary. McFarlane (A.), J. Pharmacop. & Exper. Therap. (Balt.), 1926, **28**, 177-207.

Unanaesthetized dogs were given large quantities of water (400 c.c.) by stomach tube, followed immediately by subcutaneous injection of 1 c.c. of pituitary fluid, with the result that diuresis was inhibited for 4 to 5 hours, during which there was an increase in urinary NaCl. Anti-diuresis was not effected by splanchnic sec-

tion but was overcome by oral administration of 1.5% NaCl or 5% urea solution. If no water was given pituitary produced fleeting diuresis followed by lessened secretion. Water diuresis could not be produced in etherized animals, possibly because of delayed emptying of the stomach due to pulorispasm. Injection of water directly into the gut often failed to produce diuresis, and when it occurred it could not be inhibited by pituitary. The same was true in decerebrate cats. In etherized animals, pituitary injection is followed by a short period of suppression with a subsequent diuresis of short duration. Under anaesthesia, intravenous injection of NaCl or Na_2SO_4 produced diuresis which was not inhibited by pituitary. The author believes that pituitary accelerates resorption from tubules by direct action on tubular cells and not by any vascular change. The results under anaesthesia were attributed to changes in water distribution in the tissues. The nature of the pituitary fluid used is not stated.—C. I. R.

The functions of the region of the infundibulum and the tuber cinereum and their relations to the hypophysis. Roussy (G.), Ann. de méd. (Par.), 1925, **18**, 407; Abst. Am. J. Dis. Child., 1926, **32**, 569.

Many physiological functions which were attributed to the internal secretion of the hypophysis are now considered as being dependent on centers surrounding the third ventricle. In his experiments on 149 dogs and 46 cats, Roussy has checked up earlier publications and has found new facts, which support the following conception of the role of the vegetative centers of the region of the tuber cinereum: The paraventricular nuclei contain a center for the regulation of the water metabolism; their artificial lesion produces polyuria and transient glycosuria. Other tuber nuclei regulate the fat metabolism; their lesion is followed by Froehlich's syndromes, which could not be produced merely by removing the hypophysis without a lesion of the tuber cinereum. The only function now attributed to the hypophysis (its anterior lobe) is the regulation of the growth of the skeleton, which could not be influenced by artificial lesions of the tuber region.

The effect of the acidity of the solvent on the stability of the active principle of the infundibulum. Stasiak (A.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, **28**, 1-8.

An investigation of the stability of oxytocic activity. The author reports that infundibular extracts prepared by quickly boiling and fractional sterilization, with acetic acid in varying concentrations with pH ranging from 7.0 to 3.4 showed no loss of activity. Similar extracts prepared with hydrochloric acid with pH=2.6 showed 90% deterioration, but HCL at pH of 4.6 showed no deteri-

oration as compared to standard pituitary preparation (Smith and McClosky). Extracts made by either method when treated with alkali lost all activity, hence the author concludes that there is no appreciable histamin formation. He further concludes deterioration is not a function of the nature of the acid, but more probably of the pH.—C. I. R.

Fatty atrophy from injections of insulin. Barborka (C. J.), J. Am. M. Ass. (Chicago), 1926, **87**, 1646-1647.

In two cases it was found that localized atrophy of subcutaneous fat may occur at the site of repeated injections of insulin. By varying the site of injection frequently and taking pains to spread the injected fluid widely, it may be possible to avoid such lesions.
—Author's Summary.

The effect of insulin on the dextrose consumption of perfused skeletal muscle. Best (C. H.), Proc. Roy. Soc. (Lond.), 1926, **99B**, 375-382.

Though several workers previously have presented some evidence that insulin accelerates the rate of disappearance of dextrose in perfusion experiments, the work was repeated with a more efficient apparatus. The perfusion apparatus of Burns and Dale (Jour. of Physiol., in press) was used. There were three experiments in which the hind quarters of cats were perfused with defibrinated blood to which dextrose and insulin were added. In the first experiment the weight of the perfused tissue was 1248 g. The hour before insulin 376 mg. of glucose disappeared, while in the hour after insulin was added 643 mg. disappeared. During the second experiment 620 g. of glucose disappeared as against 324 mg. the hour before. The tissue weighed 652 g. With 728 g. of tissue in the third experiment 324 mg. of glucose disappeared in the hour before insulin, as compared with 620 mg. in the hour after the addition of insulin. The rate of the disappearance of glucose is more rapid after insulin has been added. There was very little disappearance of sugar when the tissue was eliminated from the circulation. The removal of the glucose from the blood used for the perfusion was dependent on the metabolic activity of the skeletal muscles.—E. Larson.

The influence of ions on the effect of insulin on deoxidizable urine carbon. Bickel (A.) & Kauffmann, München. med. Wchnschr., **72**, 976; Chem. Zentr, 1925, **2**, 1182; Abst. Chem. Absts., 1926, **20**, 2189.

Experiments indicate that insulin is active under normal conditions only when the body has available a definite mixture of mineral

substances. The action of insulin is therefore closely related to the action of ions. The action of the insulin is located at the boundary surfaces of the cells and metabolic disturbances in diabetes consist partially at least in the inability of sugar to penetrate the cells in sufficient quantity. The increased elimination of mineral substances in avitaminosis is suppressed by insulin, and in general the less the carbon eliminated, the smaller the amount of salts eliminated.

Effect of insulin and pituitary extract on gastric secretion. Cascao de Anciaes (J. H.), Compt. rend. Soc. de biol. (Par.), 1926, **95**, 313; Abst. J. Am. M. Ass., **87**, 1516.

Ten persons, healthy or with a stomach disease, were given insulin before a test meal. In seven cases there was an increase of the hydrochloric acid paralleling that of the total acidity. The phenomenon was manifest within the second hour after the meal, and most pronounced in those with gastric neurosis of the hypervagotonic type. An increased gastric secretion appeared before an exaggerated appetite. Evidently the action of insulin is not psychic but exerts its influence on the vegetative nervous system. Thus the fact that many emaciated persons gain in weight under insulin treatment may be explained by the frequency of neurosis of the vegetative type in these patients. Pituitary extract reduced the acid secretion, also apparently through action on the vegetative system.

Insulin in treatment of denutrition. Coro (A. J.), Rev. de med. y ciruj. de la Habana, 1926, **31**, 373-378; Abst. J. Am. M. Ass., **87**, 1520.

Coro's experience in ten cases has confirmed the prompt benefit and gain in weight experienced under small doses of insulin (3 to 10 units) in extreme denutrition in children and adults, rebellious to repose and forced feeding. The weight increased from 74 to 86 pounds in two months in a girl aged 11, and from 90 to 102 pounds in one month in one young woman—a total of six and five injections.

Edemas and insulin. da Fonseca (F.), Compt. rend. Soc. de biol. (Par.), 1926, **95**, 343; Abst. J. Am. M. Ass., **87**, 1516.

Five patients with edema, three of renal origin, were given the same diet and the same amount of liquids, with and without insulin. In these cases da Fonseca found that the amount of the urine was increased under the influence of insulin.

Experiments on diabetes and insulin action. IV. Inhibition of glucose uptake by the erythrocytes through diabetic plasma (Untersuchungen über Diabetes und Insulinwirkung. IV. Ueber Hemmung der Glucoseaufnahme von seiten der Erythrocyten durch

diabetisches Plasma). Häusler (H.), Arch. f. d. ges. Physiol. (Berl.), 1926, **213**, 602-615.

Erythrocytes take up on the average 30 per cent less glucose from the plasma of adrenine-diabetic rabbits and of diabetic men than from that of non-diabetics.—A. T. C.

The effect of exercise on insulin action in diabetes. Lawrence (R. D.), Brit. M. J. (Lond.), 1926, **1**, 648.

The clinical results of two cases of diabetes mellitus as influenced by exercise were considered. That exercise would reduce glycosuria and blood sugar in diabetes mellitus has been known for many years. The first patient led a sedentary life during the week, but played tennis on Sunday. During the week 16 units of insulin were needed to keep his urine sugar free and reduce his blood sugar to 0.1%. When three or four sets of tennis were played only eight units were required. The second patient was a gardener who, during the fall and winter months, was receiving 10 units of insulin in the morning and 6 units in the evening. In the spring and summer when the most work was done as well as playing cricket in the evening, only 6 units of insulin were required. The immediate effect of exercise is to increase the fall of blood sugar caused by the insulin, but this action only occurs during the maximum period of activity of the insulin (1-4 hrs. after injection). The author concludes that exercise not only increases the power of activity of circulating insulin, but actually causes sugar to be burned which depletes the carbohydrate stores of the body. With the increase of exercise the amount of insulin should be reduced. The patients on insulin treatment should learn to decrease the amount of insulin before unaccustomed exercise.—E. Larson.

On the inverse change between the concentration of glucose and chloride in the blood. Ni (T. G.), Am. J. Physiol. (Balt.), 1926, **78**, 158-167.

Histamine causes in dogs a fall of blood chloride (consequent on gastric secretion) which is frequently accompanied by a rise in sugar. This inverse change is more marked in the plasma than in the corpuscles. Similar inverse changes may also be obtained by means of sham-feeding or by partial obstructions of the intestines, although the inverse relationship is not in invariable proportion. Either denervation of the adrenal glands or double adrenalectomy prevents the rise in blood sugar by histamine, without materially affecting the fall in chloride. After total extirpation of the pancreas, the subsequent hyperglycemia is accompanied by a marked lowering of the blood chlorides. An injection of insulin, which brings the sugar down, raises the blood chloride, in diabetic

as well as in non-diabetic dogs. Our results would suggest that while the increase in the blood sugar which accompanied a primary decrease in chlorides is probably the result of reflex stimulation of the adrenals, i. e., the sugar change is not dependent on the chloride, the fall and the rise of blood chloride which occurs in pancreatectomized dogs, or normal dogs after the injection of insulin (primary movement of sugar), are directly related to the sugar fluctuations and may be due to an effort at osmotic and other compensations.—Author's summary.

An address on diabetes. Rabinowitch (I. M.), Canad. M. Ass. J. (Montreal), 1926, **16**, 1021-1028.

A general review chiefly from the clinical standpoint.

—A. T. C.

Hypoglycemic coma due to repeated insulin overdosage. Sevringhaus (E. L.), Am. J. M. Sc. (Phila.), 1926, **172**, 573-580.

The clinical observations made on five patients who had unusual psychic reactions to repeated overdoses of insulin are given. The important findings are amnesia, disorientation, aphasia and sleepiness. The depression was so complete and with such inadequate premonition that in one case a gastric disturbance caused vomiting and a fatal aspiration pneumonia. These unusual reactions were observed only in cases where hypoglycemia occurred at such short intervals within a day that there was little opportunity to replenish glycogen stores. The danger of depending on sugar intake by mouth when gastric stasis may be a complication of the diabetic picture is evident.—Author's Abstract.

An unusual blood sugar finding during an insulin reaction. Smith (M.), Boston M. & S. J., 1926, **195**, 663-664.

The blood sugar reading by the Folin and Wu method was zero.—J. C. D.

The effect of insulin on the respiratory exchange of decerebrate and decapitate cats. Taylor (A. C.) & Olmsted (J. M. D.), Am. J. Physiol. (Balt.), 1926, **78**, 17-27.

In a decerebrate cat injected with insulin, in which there were no complications through respiratory distress, the respiratory quotient rose, but the O_2 consumption remained level until just before convulsions, when it fell. After a series of convulsions the respiration fell, while the O_2 consumption and ventilation rose. In decapitate cats injected with insulin, the O_2 consumption generally falls temporarily either just before or at the time when hypersensitivity is observed. A rise in O_2 consumption is usually associated with muscle spasms. The respiratory quotient shows a definite rise

to a maximum immediately before convulsions. During convulsions there is a fall in the respiratory quotient. The severity of symptoms is associated with the magnitude in the changes in the respiratory quotient. In decapitate cats injected with curare and insulin the changes in O_2 consumption show variations which do not follow any definite rule. The most striking change is the rise in respiratory quotient nearly to unity. When the caloric output is calculated it is found that the total metabolism does not change in any marked degree except when convulsions occur. There is usually a fall in the caloric output just before the convulsions. The proportion of the caloric output due to combustion of carbohydrate, however, rises from zero or a low level, until just before time for convulsions it often accounts for the total caloric output. The same marked rise in the proportion of the caloric output due to carbohydrate combustion is seen following the injection of insulin in the curarized animals.—Author's Abstract.

The antagonistic action of insulin and hypophysis upon water economy (Die antagonistic wirkung des insulins und hypophysen hormons auf den wasserhaushalt). Vollmer (H.) & Serebrijski (I.), Biochem. Ztschr. (Berl.), 1925, **164**, 1.

Pituglandol and insulin each has an antidiuretic action separately, but when given in combination produces lesser water retention than with pituglandol alone. The authors think that insulin hinders the action of pituitary, especially the renal components of this action, the blocking of the kidneys. With simultaneous action of both hormones, the blood dilution fails to appear. Primarily the water imbibed during the experiment is stored in the tissues and, as soon as the hormone effect is gone, the tissue water enters the blood vessels and then acts as a stimulant on the kidneys. The inhibiting effect of the insulin on pituitary can be explained on a central basis. The experiments consisted of administering 1500 c.c. of water to patients and then examining the urine every hour for specific gravity, amount passed, and sodium chloride content, while the blood was examined for concentration, serum protein and hemoglobin content. Pituglandol was injected at the beginning of the experiment and two hours later. Insulin was injected on the third day and insulin and pituglandol later.—M. B. Gordon.

Regulation of metabolism. II. The incretory regulation of fat mobilization (Stoffwechselregulationen. II. Die inkretorische Regulierung der Fettmobilisierung). Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, **213**, 280-286.

Insulin inhibits peripheral fat mobilization in all cases, as for example after phloridzin administration. With strong doses of insulin the inhibition may be complete. No transference of fat to the

liver takes place. Adrenaline produces similar effects only in heavy doses, and never completely.—A. T. C.

Regulation of metabolism. III. Nervous and incretory influence on fat changes in the liver (Stoffwechselregulationen. III. Der nervöse und inkretorische Einfluss auf die Umwandlung von Fett in der Leber). Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, **213**, 287-297.

Insulin accelerates fat change in the liver; at the same time glycogen increases. Also after adrenaline dosage there is rapid fat degradation and formation of glycogen in the liver.—A. T. C.

Regulation of metabolism. IV. The incretory influence on change of fat into carbohydrate in the liver (Stoffwechselregulationen. IV. Die inkretorische Beeinflussung der Umwandlung von Fett in Kohlenhydrate in der Leber). Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, **213**, 298-320.

Dogs that after phloridzin treatment are depleted of sugar and whose livers contain but traces of glycogen, but much fat, are much less sensitive to insulin than are dogs that have been for the same period starved or fed a normal diet. Symptoms of insulin-poisoning appear with each, but weaker with the former, who rapidly recover. There is a corresponding lowering of the blood sugar curve with each, but a more rapid after-rise with the phloridzin animals. These show marked depletion of the liver fat, with formation of fresh glycogen, indicating formation of carbohydrate from fat in the liver under the accelerating action of insulin. In the control animals there is no such possibility of formation of sugar from fat; insulin inhibits mobilization of peripheral fat depots. Similar phloridzinised dogs show more marked reaction to adrenine than do normal animals; adrenine also accelerates the change from fat to carbohydrate.—A. T. C.

Interesting results from use of parathyroid extract in case of osteitis deformans (Paget's disease). Bassler (A.), J. Am. M. Ass. (Chicago), 1926, **87**, 96-97; Abst. A. M. A.

Suggested by the work of Collip on parathyroidectomized dogs in which the administration of extracts of parathyroid glands raised the calcium content of the blood, this substance was employed by the author in a case of osteitis deformans with a happy result. In this case of steadily progressing Paget's disease no treatment was of any value up to the moment the parathyroid was started. Within a short time after its use was established a most marked change for the better occurred. The dose of parathyroid was 1/10 grain (0.006 gm.) after each meal.

Changes in the chemical and physical characteristics of the blood following the administration of parathyroid hormone. Cantarow (A.), Caven (W. R.), & Gordon (B.), Arch. Int. Med. (Chicago), 1926, **38**, 502-509.

In a study of ten clinical cases of pulmonary tuberculosis it was found that there seemed to be no significant change in carbon dioxide combining power or in the plasma chlorides following the administration of parathyroid hormone. There was a tendency toward increased concentration of the blood as evidenced by an increase in red and white counts, hemoglobin, and in the blood viscosity. A definite decrease in clotting time was noted in most cases. The time of most rapid coagulation corresponded in every case to the point at which the whole blood calcium was highest, rather than to the highest point of the serum calcium.—R. G. H.

Therapeutic value of parathyroid hormone. Collip (J. B.), J. Am. M. Ass. (Chicago), 1926, **87**, 908-909; Abst. A. M. A.

Collip states that the function of the parathyroid hormone is in the main related to calcium and phosphorus metabolism. It is possible that the parathyroid glands subserve other functions, and it is also possible that there may be other hormones in these glands of which we have no knowledge at present. Experimental parathyroid tetany is characterized by a lowered calcium content of the blood serum and as a rule an increase in the inorganic phosphorus. The parathyroid hormone, when administered by injection to dogs in a state of parathyroid tetany, causes the blood calcium level to be restored and the inorganic phosphorus if increased to be decreased. There is also the restoration of the animal to an apparently normal condition. There is also noted a definite quantitative relationship between the dosage administered and the calcium mobilizing effect produced. Normal dogs which have been injected with an active parathyroid extract manifest an increase in the blood serum calcium which is proportionate to the dosage administered. Overdosage effects which may result in death have been produced consistently in both normal and parathyroidectomized dogs. The main physiologic action of the parathyroid hormone as seen by the laboratory worker is that of a blood calcium mobilizer. It would therefore seem logical to conclude that the parathyroid hormone will be of definite therapeutic value in any condition in which the blood serum calcium is below the normal value. Blood serum calcium has been shown to be lowered in post-operative tetany, in spasmophilia, intropical sprue and in certain types of nephritis. Collip suggests to clinicians that a potent parathyroid extract is now available which has the specific effect of mobilizing calcium in the blood stream. If one is desirous of influencing profoundly calcium metabolism, the new hormone may be employed as the therapeutic agent.

Studies on the pathogenesis of tetany. VII. The prevention and control of parathyroid tetany by the oral administration of kaolin. Dragstedt (L. R.) & Sudan (A. C.), Am. J. Physiol. (Balt.), 1926, **77**, 314-319.

The oral administration of kaolin in amounts of from 50 to 200 grams was found to be effective in controlling parathyroid tetany and in preserving the life of completely thyro-parathyroidectomized dogs. It is suggested that this effect of kaolin is due to the absorption of toxic products of bacterial growth in the gastro-intestinal tract and to the predominance of an aciduric intestinal flora which it brings about. These experiments are interpreted to support the views that parathyroid tetany is an intoxication and that the responsible toxic substances in non-pregnant animals arise chiefly in the gastro-intestinal tract as a result of bacterial proteolysis.—Author's summary.

The effect of parathroid extract and liver extract on the hypertension produced by guanidine compounds. Major (R. H.) & Buikstra (C. R.), Johns Hopkins Hosp. Bull. (Balt.), 1925, **37**, 392-399.

The authors found that the elevation of blood pressure produced by guanidine compounds was abolished by the use of parathyroid extracts and liver extracts. The parathyroid extracts used were prepared by the method of Hanson and Collip. The liver extract employed was prepared by the method of acid alcohol extraction and alcoholic fractionation. The dose of parathyroid extract and liver extract which produced experimental hypertension had only a slight effect upon normal blood pressure.—R. H. Major.

A case of sub-parathyroid tetany treated with Collip's extract of parathyroid. Monteith (J. R.) & Cameron (A. T.), Canad. M. Ass. (Montreal) J., 1926, **16**, 1104-1106.

Recurring exophthalmic goitre led to a second thyroidectomy, and though care was taken by the surgeon to conserve sufficient thyroid and parathyroid tissue tetany developed within three or four days of the second operation, and, later on, symptoms of hypothyroidism. The latter was controlled adequately by desiccated thyroid. The former was partially controlled by calcium lactate by mouth, and completely by injections of Collip's extract. Eighty-two days after this operation with withdrawal of the extract and lactate for a sufficient period the serum calcium fell to the low level initially reached indicating that at that period there was no hypertrophy of any parathyroid tissue that remained. Within two months of this date, on calcium lactate therapy alone, apparently such a hypertrophy occurred, since the serum calcium returned to normal,

and discontinuance of the lactate was followed neither by lowering of the serum calcium nor by any clinical symptoms of tetany.
—A. T. C.

Effect of parathyroid feeding on the thyroid. Woodman (Dorothy), J. Physiol. (Lond.), 1926, **61**, 557-561.

A report of experiments in feeding young and adult rats of both sexes with 0.02 gm. daily of desiccated parathyroid from 2 to 5 weeks. Both the thyroid and parathyroid glands were examined grossly and microscopically. There was no marked change in the parathyroids of rats so fed as compared to those of controls. The thyroids presented an inactive appearance manifested by increased colloid and distended vesicles. The author believes this suggests that the two glands are antagonistic in function, since there were no changes induced resembling those following thyroid feeding as would be the case if the function of the parathyroids is to replace the function of the thyroids.—C. I. Reed.

Extirpation of the parathyroid gland in the domestic fowl. II. Report. Yamaoka (H.), Acta scholae med, univ. imp. (Kioto), 1925, **8**, 209-240.

The extirpation of parathyroid tissue is followed by a more or less marked increase in the electric excitability of the peripheral motor nerves, although not to the same extent as in the mammalia. As a rule, no alteration of the normal sequence of the various responses results, but the A. O. C. is more marked than the A. C. C. The increased electric excitability of the peripheral nerve is independent of the charge from the central nervous system. It occurs whether the nerve be cut before or after the removal of the parathyroids and persists till degeneration sets in. The electric excitability of muscle to direct stimulation is increased after parathyroidectomy, although not to the same extent as that of the nerve. This is chiefly due to an increased electric excitability of the neural structures in the muscle, since it is generally abolished by a dose of curare sufficient to block nervous impulses. In the disturbance occurring after parathyroidectomy, the increased electric excitability of the peripheral motor nerve is somewhat proportionate to the intensity of the symptoms due to the condition of the central nervous system. The extirpation of the parathyroid gland produced no detectable symptoms of the central nervous system in a large majority of our cases.—Author's abstract.

Extirpation of the parathyroid gland in the domestic fowl. Third Report. Yamaoka (H.), Acta scholae med. univ. imp. (Kioto), 1925, **8**, 241-263.

The administration of guanidine salts to domestic fowls induces symptoms, which are almost identical with those of tetania

parathyreopriva. At the same time the hyperexcitability of the peripheral nerves, which also occurs after removal of the parathyroid, is induced by the administration of the drug. The hyperexcitability resulting from the lack of the parathyroid, therefore, may be due to the action of guanidine, which is increased in the blood under that condition. After several successive days the electrical excitability decreases again. In fowls, the hyperexcitability of the nervous system produced by guanidine administration is restored by the injection of calcium lactate. As the experiments above described show, the clinical symptoms and electrical hyperexcitability on the peripheral nerves in fowls after the extirpation of the parathyroid, or after the administration of guanidine salts, are slighter and lower than those in mammalia under the same conditions.—Author's abstract.

The influence of thymus feedings on amphibia and mammals. Romeis (B.), Klin. Wchnschr. (Berl.), (1926), **5**, 975-977.

Metamorphosis and subsequent growth in tadpoles was inhibited by feeding a diet made up exclusively of thymus. Controls, fed liver only, did not show this retardation. Similarly one series of young rats were fed only thymus and water while controls were fed liver and water. The thymus-fed rats showed signs of marked inhibition of both growth and development eventually developing cachexia, which was soon terminated by death. The males seemed slightly more susceptible than the females. The controls did not show these changes. There was retardation of bone growth, hypoplasia of the lymphoid tissues and striking involution of the thymus. The changes in the thyroid and hypophysis were less marked. The heart, lungs, spleen, kidneys, and suprarenals were smaller than in the controls. There were very slight differences between the weights of the brains and the skulls of the thymus-fed as compared with the liver-fed rats. The ovaries and testes of the thymus-fed rats showed striking indications of arrested development. In the females the cyclic changes were not seen, while they occurred regularly in the controls of this sex.

It was found that all these changes could be prevented if vitamin-rich vegetables were added to the thymus feedings. The author therefore believes that the inhibitory effects observed were due not to a specific hormone present in thymus tissue, but to a lack of vitamin substances essential for development and growth.

No experimental data are included in the article.—S. Shapiro.

Diet and action of internal secretions. VI. The action of thyroxine during feeding with diets of different composition (Ernährung und Inkretwirkungen. VI. Thyroxin-Wirkung bei Verfütterung verschieden zusammengesetzter Nahrung). Abderhalden (E.) &

Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1926, **213**, 328-335.

The action of thyroxine on metabolism depends greatly on diet. Rats fed carbohydrate-rich, protein-poor diet under dosage of thyroxine show but slight (14%) increase in gas-metabolism, which rapidly returns to normal. On protein-rich diet the effect is much greater (an average increase of 37%) and lasts over 9 days. On fat-diet intermediate results are obtained.

Goiter patient unsuited to thyroidectomy. Bartlett (W.), J. Am. M. Ass. (Chicago), 1926, **87**, 1279-1282; Abst. A. M. A.

There are certain persons who simply cannot be restored to a condition in which thyroidectomy seems advisable. The author divides them into four classes: those who die of thyrotoxicosis; those who are dismissed as hopeless; those who are intolerant of restraint, and those who die of intercurrent diseases. The first class are not saved from death by compound solution of iodine, roentgen-ray treatment injections and ligations. In Bartlett's clinic, six criteria determine the patient's fitness for operation. They refer to heart condition; blood nitrogen; metabolic rate; patient's weight; self-control, and blood pressure. As far as the heart is concerned, there may be transient fibrillation, but there must be no organic congestion and the rate must not be too fast, while the electrocardiogram should conform to ordinary standards. As far as blood nitrogen is concerned, it must be under 50. The metabolic rate should be about 40 plus, although a falling rate of 50 plus is much more desirable than a rising rate of 40 plus. As to regaining of weight, it should be at least 50 per cent of what the patient has lost in order for conditions to be ideal in this particular. The regain of self-control is exemplified in many ways, the best of which is a spirit of cooperation. It is a favorable sign for a patient to urge the operator to continue postponement of the operation as long as his judgment dictates; whereas, on the other hand, the patient who urges him on all occasions to operate is likely to be a victim of a severe postoperative explosion. The blood pressure, in order to be satisfactory, should be fairly high, with a wide pulse pressure even though there is some shading. Bartlett suggests 140/65-55 as being about the average. A low operative mortality can result only from adequate preparation and a correct choice of patients. These two considerations, if any, justify the treatment of goiter as a specialty, much as the treatment of central nervous lesions has become a recognized specialty in surgery.

The elimination of the iodine in the urine in normal patients and in exophthalmic goiter. Cattell (R. B.), Boston M. & S. J., 1926, **195**, 69-71.

Normally 70% of the iodine given is excreted in the first 24 hours. In the thyroid cases the elimination is less. The authors suggest that the usual 250 mg. daily dose is excessive for supplying the needs of the thyroid. Tables of excretion are given.—J. C. D.

Specific influence of the thyroid gland on hair growth. Chang (H. C.), Am. J. Physiol. (Balt.), 1926, **77**, 562-567.

Albino rats deprived of thyroids show a retardation of hair growth. Upon feeding suitable amounts of thyroid (0.5 to 0.7 gram) in the dose of 0.03 gram per day, hair grows normally. Undernourished animals with intact thyroids show a similar retardation of hair growth. Thyroid feeding to such animals kept on the chronic starvation diet improves the hair growth in spite of the further decreased body weights caused by excessive catabolism in addition to the originally deficient anabolism. This proves the specific influence of the thyroid gland on hair growth. Feeding of thyroid accelerates the hair growth in some normal animals, while in others no such result was obtained. Further experiments are required to determine whether the refractory animals have thyroids functioning at a rate optimum for hair growth. Excessive amount of thyroid given by repeated administrations over a long period of time retards the hair growth of the normal animal due to the secondary nutritional upset of increased catabolism. Further work on the study of the constituents of the thyroid gland responsible for this hair reaction has been in progress in order to determine whether or not this hair reaction can be used as a functional test of the thyroid gland.—Author's abstract.

Nephrosis of thyroid origin. Davidson (J. R.), Canad. M. Ass. J. (Montreal), 1926, **16**, 1059-1063.

Three cases are reported, each showing different peculiarities The first was a case of nephrosis with mild hypothyroidism, which was greatly improved by thyroid treatment, relapsed after cessation of the treatment, and finally was apparently spontaneously cured, the patient now being—as shown by clinical examination—a normal young woman. The second, a case of nephrosis with marked hypothyroidism and hypoparathyroidism, was also greatly benefited by the combined administration of desiccated thyroid and Collip's parathyroid extract, but finally died of an intercurrent infection. The third was a case of hypothyroidism and apparent hyperparathy-

roidism (serum calcium above normal), markedly emaciated, with apparent dehydration of tissues. Under thyroid treatment the basal metabolic rate returned to normal, the patient gained weight, and the serum calcium fell to normal figures. Continued treatment led to a metabolic rate above normal with continued gain of weight. Cessation of thyroid administration did not stop these progressive changes, and in the 18 days thereafter the rate rose from plus 14 to 65 per cent, and the weight increased from 100 to 135 lbs. In the next 28 days the rate fell to plus 24 per cent, but the weight increased to 153 lbs. During this period there was no clinical symptom of hypo- or of hyper-thyroidism, and no pituitary or other explanatory change could be demonstrated. It is suggested that nephrosis associated with pregnancy may also be due to slight thyroid deficiency, and that in this condition small thyroid doses may be of value.—A. T. C.

Thyroid hypertrophy and pregnancy. Davis (C. H.), J. Am. M. Ass. (Chicago), 1926, **87**, 1004-1009; Abst. A. M. A.

Approximately 41 per cent of the last 520 women examined by the authors in early pregnancy had visible hypertrophy of the thyroid. Eight of these patients have returned with typical symptoms of toxic goiter within fourteen months after delivery. Small doses of iodine have been administered during pregnancy, but none after delivery. No patient has returned with hyperthyroidism earlier than four months after delivery. Overwork, worry and other forms of nervous strain appear as contributing causes in each case. The use of iodine during pregnancy by women who live in goiter districts is advocated as a prophylactic measure, unless they have adenoma of the thyroid. Iodine hyperthyroidism is recognized as a possibility, but thus far has not been observed. The average metabolic rate of nine women with normal thyroids at term was + 2.4 per cent. Their average after delivery was —1.3 per cent. The average rate of seven women with simple hypertrophy was + 22.1 per cent before term, with a later drop to + 3.1 per cent. The average rate of nine women believed to be of the hyperthyroid type was + 32.2 per cent before delivery, with a drop eleven days post partum to + 8.9 per cent. With the exception of two patients in the last group, these patients took small doses of iodine during the last months of pregnancy. Patients previously operated on for toxic goiter are usually benefited by taking small doses of iodine during pregnancy. One such patient in the small group under observation apparently could not tolerate iodine. One patient had a successful operation for toxic adenoma of the thyroid in the fourth month of pregnancy

and later took iodine. One patient with a history of toxic adenoma took iodine during pregnancy with apparent benefit, although she had a metabolic rate of + 86 at term. She was successfully operated on twenty days post partum. The baby was continued at the breast, and complementary feedings were stopped six days after the operation. The subsequent history of both mother and infant is very satisfactory. Prolonged nausea and vomiting in one case was evidently due to a crisis of exophthalmic goiter. The metabolic rates on this patient are given. She had a rate of + 81 per cent ten days before delivery. Her nausea was lessened by the use of iodine. Patients with toxemia of pregnancy had low readings. Three with edema and little or no albumin had lower readings than the single patient with high blood pressure, albumin and casts but no edema. Comparative studies of the blood calcium and thyroid function, as indicated by the basal metabolic rate, show no relation between the milligrams of calcium in each hundred cubic centimeters of serum and the metabolic rate. The calcium determinations in twenty-four women with uncomplicated pregnancy showed an average of 9.97 mg. before delivery and 10.5 eleven days post partum. Most of these women had taken calcium salts in addition to their food. The average for the patients with thyroid hypertrophy was slightly higher than the average for the women with normal thyroids, but a small series does not warrant conclusions. Three patients with toxemia of pregnancy showed a lowering of the calcium post partum, while the normal patients usually showed an apparent increase within eleven days. The use of cod liver oil and ultraviolet irradiation did not appear to increase the blood calcium in the few cases studied.

Thyroid therapy and thyroid tolerance in chronic nephrosis. Epstein (A. A.), J. Am. M. Ass. (Chicago), 1926, **87**, 913-918; Abst. A. M. A.

Epstein calls attention to the enormous tolerance of patients with nephrosis for thyroid substance and thyroxin. He has found that in chronic nephrosis the amount of thyroid or thyroxin necessary to produce a therapeutic effect is most extraordinary. For example, daily doses of from 1 to 4 gm. (15 to 60 grains) of thyroid are often required over long periods of time to elicit a metabolic response. The fate of the thyroid and thyroxin in chronic nephrosis has not been determined by Epstein; whether the unusual tolerance exhibited by these patients is due to increased excretion, inactivation, or lack of absorption by the tissues is still problematic. The problem in the treatment of chronic nephrosis is threefold, namely: (1) To replace the protein loss of the blood plasma which results

from the albuminuria and which plays so large a part in the retention of water and the formation of edema. This is best accomplished by feeding a high protein diet; that is, 2 and 3 gm. of protein per kilogram of body weight. (2) To compel the tissues to utilize protein and incidentally to reduce the lipoidemia. This, too, is often accomplished by a liberal protein, but fat-poor diet. The administration of thyroid aids in attaining this desideratum. (3) To reestablish normal metabolism. When high protein feeding fails to accomplish this, the institution of thyroid is definitely indicated. Epstein's method of treatment is as follows: When the preliminary high protein feeding fails to give any therapeutic result, such as elimination of the edema, control of the albuminuria, and change in the chemical reaction of the blood, the use of thyroid is begun. The initial dose is usually small, from ½ to 1 grain (0.03 to 0.065 gm.) three times a day. In many instances this dose may be sufficient to enhance the effect of the high protein diet in attaining its therapeutic success. As a rule, however, much larger doses are needed. The amount of thyroid is therefore rapidly increased until a daily dose of 15 grains (1 gm.) is reached. If such a dose fails to give any indication of effectiveness, it is immediately doubled and administered for from five to seven days. If this in turn does not give therapeutic results, the use of thyroxin is resorted to. It is given intravenously, the initial dose being from 5 to 10 mg. This dose may be repeated at intervals of from five to ten days until definite effects are observed. The beneficial effect is indicated by increased diuresis, diminution in the albumin output and decrease in the lipoidemia. While increase in pulse rate and elevation of temperature occasionally follow the use of thyroxin, no toxic symptoms develop as long as the lipoidemia persists. The oral administration of thyroid in large doses occasionally causes gastric distress, such as anorexia and nausea, and in such cases the use of thyroxin is resorted to at once. As soon, however, as therapeutic results are evidenced, the dose of thyroid and thyroxin is reduced, the main guide being the lipoidemia. Thyrotoxic symptoms have not been observed thus far, in spite of the enormous doses of thyroid and thyroxin used, a fact which would seem to indicate that untoward symptoms are not likely to occur prior to a favorable turn in the clinical course of the disease.

The rôle of the thyroid apparatus in the growth of the reproductive system. Hammett (F. S.), Am. J. Physiol. (Balt.), 1926, **77**, 527-547.

A study is given of the normal course of development of the

reproductive systems of male and female albino rats which serves as a basis of determination of the rôle of the thyroid apparatus therein. An improvement in dietary and environmental conditions brings about an earlier sexual maturity. The reproductive system of the male reaches maturity at an earlier age than does that of the female. The development of the uterus lags behind that of the ovary. The sociological implications of these findings in their relation to man are briefly indicated. There is no apparent specific relation between the growth of the reproductive system of either sex and thyroid or parathyroid activity. The growth retardation which occurs is attributable to the general metabolic disturbance which results in a condition of essential undernutrition, and the dependence of the parts of the body on the effectiveness of the growth processes of the whole. The ovary and the uterus follow the body weight in its changes in growth retardation after glandular removal at the stated ages. The degree of retardation is of the same order of magnitude until the practical completion of the pubertal adjustment, when the surge in ovarian incretory activity determines a relatively increased sensitivity of the reproductive system. This is evidence for an ovary-thyroid and ovary-parathyroid incretory relationship, the basis of which lies in the ovary. Evidence is had that the incretory activity of the ovary conditions the response of the uterus to the glandular deficiencies, when and only when, the latter has reached the period in which it attains its full functional maturity. The testis and epididymis are less sensitive to thyroid and parathyroid deficiency than is the body as a whole. Prior to the pubertal adjustment they do not follow the body weight change with change in age at time of glandular removal. After the readjustment they show a direction of change like that of the body. The difference is attributable to a difference in the relative proportion of total growth represented by growth by increase in cell number. The pubertal adjustment decreases this difference and hence the growth reaction of the reproductive system approximates in kind that of the body as a whole. The marked concordance of testis and epididymis response both in degree and kind is attributable to the close functional and structural association between the two. The relations outlined are consistent with the pertinent coefficients of correlation. Evidence is had that a factor in the greater incidence of thyroid disturbances in girls and women as compared with boys and men, is the presence of a greater incretory relation between ovary and thyroid, than is evident between testis and thyroid. The relations of the growth responses of the various organs to those of the body as a whole and to each other, subsequent to glandular removal at the different ages, confirm the belief as to the

rôle of the thyroid apparatus in growth developed in an earlier study.—Author's abstract.

Exophthalmic goiter in childhood. Helmholz (H. J.), J. Am. M. Ass. (Chicago), 1926, **87**, 157-162; Abst. A. M. A.

Thirty cases of exophthalmic goiter occurring in children less than 15 years old are reviewed by Helmholz. Compound solution of iodine, administered in doses of from 5 to 10 minims (0.3 to 0.6 cc.) three times a day, reduced the basal metabolic rates and toxic symptoms very markedly. It made preliminary operations unnecessary in the last eleven cases. Of twenty-four patients operated on, two died, one in crisis twenty-four hours after operation and the other from bronchopneumonia one week after operation. The duration of the symptoms, which varied from six months to eight years, indicates that frequently this disease is not recognized early or its seriousness is not appreciated. The patients came largely from Minnesota, Iowa, Illinois and Wisconsin, in the order named. Tachycardia was noted in 100 per cent of the cases. The thyroid gland was definitely enlarged in all but two cases. All but two patients complained of nervousness. Emotional instability was perhaps the most marked feature. Exophthalmos was definite in twenty-five of the thirty cases, and in one of the remaining five there was the characteristic stare.

Goitre in children—a study of treatment. Kitchen (H. D.), Canad. M. Ass. J. (Montreal), 1926, **16**, 923-931.

Three groups each of 24 children with goitre were treated respectively with desiccated thyroid (1 to 2 grains per day), Lugol's solution, and expectantly. After from three to six months' observations the following conclusions are drawn (it has been noted that the amount of improvement obtained in the first three months of treatment indicates the degree of result to be obtained by a further continuation of therapy): Desiccated thyroid produced a greater number of marked improvements and less failures than did iodine (Lugol's solution) or the expectant therapy. Iodine treatment produced much better results than those occurring in the untreated cases. No cases of iodine hyperthyroidism resulted from the use of Lugol's solution, and continuous use of desiccated thyroid produced no untoward effects. The necessity of frequent examination of the patient on thyroid treatment is insisted on though clinical observation is sufficient and frequent basal metabolic rate determinations are not necessary.—A. T. C.

Quadriceps test for myasthenia of thyroidism. Lahey (F. H.), J. Am. M. Ass. (Chicago), 1926, **87**, 754; Abst. A. M. A.

A test is described by Lahey which is said to be of considerable value in diagnosis of hyperthyroidism based on the well established weakness of the quadriceps femoris in this disease. The patient sits well forward on the edge of a straight chair and holds the leg out at right angles to the body. In very few cases of thyroidism of any marked degree of intensity will it be possible for one to maintain the leg in this position more than twenty-five or thirty seconds, while in the majority of cases not affected by thyroidism the leg can, with any real effort, be held in this position for approximately one minute.

Substernal goiter. Lahey (F. H.), J. Am. M. Ass. (Chicago), 1926, **87**, 1282-1286; Abst. A. M. A.

The author contends that any tendency for a goiter to become substernal is an indication for its removal. The ill effects of substernal goiter are primarily deviation, flattening, and narrowing of the trachea. The diagnosis by means of roentgen-ray and physical examination may be made with considerable certainty. Surgical removal may be accomplished in a great majority of cases even when the substernal mass has passed downward behind the arch of the aorta, but an operative procedure of this magnitude would be unnecessary if the early adenomas and cysts were removed while still only tending to become intrathoracic. In an experience with more than 200 substernal goiters, Lahey has succeeded in accomplishing their removal without removal of the manubrium in all except two cases. The technical features of removal of substernal goiters are the prevention of hemorrhage and the protection of the pleura, thoracic duct, and recurrent laryngeal nerve, three structures which form the walls from which the intrathoracic mass must be separated, the prevention of tracheal collapse, and insufficient air intake during removal and the extrication of the mass. These steps may all be accomplished by gentle manipulations in the proper lines of cleavage and with the cooperation of an anesthetist experienced in the methods of aiding these patients in getting air during the time tracheal pressure is being made during the manipulative removal of the mass. This has been accomplished by a tight mask and the introduction of oxygen into the lungs by pressure.

Myxedema simulating pernicious anemia. Meulengracht (E.), Ugesk. f. Laeger (Copenhagen), 1926, **88**, 721; Abst. J. Am. M Ass., 1926, **87**, 1252.

Meulengracht's patient was a young woman presenting the clinical picture of chronic pernicious anemia with a rather torpid course. The basal metabolism was found 40% below normal, and, under thyroid treatment recovery was prompt and complete. The slight tendency to a myxedema aspect had not been recognized until the basal metabolism had given the clue. The achylia, blood changes, paresthesias and leukopenia observed are common to both pernicious anemia and thyroid deficiency.

Pregnancy complicating exophthalmic goiter. Mussey (D.), Plummer (W. A.) & Boothby (W. M.), J. Am. M. Ass. (Chicago), 1926, **87,** 1009-1011; Abst. A. M. A.

To elucidate the question of a possible relationship between exophthalmic goiter and adenomatous goiter with hyperthyroidism and pregnancy, as well as to determine their clinical effect on one another, a study has been made by the authors of forty-two women whose pregnancy was complicated by these diseases. There was no evidence that pregnancy influenced the course of exophthalmic goiter. Serious additional complications were not more frequent than is usual in either condition alone, and therapeutic abortion was not necessary. Both the course of pregnancy and the maternal and fetal mortality were not appreciably affected as the result of the syndrome due to exophthalmic goiter or to adenomatous goiter with hyperthyroidism, nor, on the other hand, did the pregnancy render the control of these two diseases noticeably more difficult.

The influence of anxiety states on the thyroid gland. Newburgh (L. H.) & Camp (C. D.), Am. Clin. Med. (Balt.), 1926, **4,** 1006-1011.

Abnormalities other than lesions of the pancreas are capable of disturbing the carbohydrate metabolism. The following case record shows how a mental disturbance may upset the metabolism of carbohydrate in such a way as to simulate diabetes mellitus.

Case record: Patient complained of the usual diabetic symptoms, and in addition a variety of pains and nervousness. Progressive loss of memory was noted. For two years there was palpitation, shortness of breath and precordial pain. Urine, on nonrestricted diet, contained glucose. Glucose tolerance test gave the following readings:

Fasting	0.100 per cent
First hour	0.232 per cent
Second hour	0.242 per cent
Third hour	0.188 per cent

Physical examination was negative except for very slight enlargement of the thyroid gland. Pulse rate 106. She was given the usual diabetic treatment and discharged on a diet yielding 2200 calories, with a total glucose value of 90 grams. She remained sugar-free four months and gained weight, but returned complaining of more fatigue and increase in her nervous disturbances. She had recently had several severe attacks of palpitation and choking, ending in unconsciousness. Her condition suggested toxic adenoma, and this suggestion was borne out by four determinations of the basal metabolic rate, with the following readings: 20, 38, 36 and 35 per cent above normal, but she did not show exophthalmos, tremor or definite palpable abnormalities of the thyroid gland. She was subjected to psycho-analysis. It was found that the seizures of which the patient complained were thought by her to indicate diabetic coma and approaching death. During her late girlhood she was compelled to remain away from school to nurse her sick mother. During this time an episode had occurred which the patient feared would cause her mother's death. Subsequent death of her mother increased the emotion. She finally succeeded in repressing this extremely painful thought, and was apparently quite well until another emotional conflict arose shortly before she began having symptoms four years ago. The conflict involved an ethical question and was associated with the former effect. When a doctor told her that she had diabetes she had a basis to transfer her anxiety to her own health, thus further covering up the original cause of the trouble. She was easily convinced that she could not have been the cause of her mother's death, and during this period her metabolic rate gradually fell to -4%. Since then it has been normal. She was placed on a non-restricted diet and the urine remained sugar-free. Her glucose tolerance curve at this time showed:

Fasting	0.083 per cent
After one hour	0.157 per cent
Two hours	0.108 per cent
Three hours	0.077 per cent

We have, therefore, in this case a demonstration that emotional disturbance may produce the standard picture of diabetes mellitus, with its large appetite, loss of weight, weakness, glycosuria and characteristic tolerance curve. The change in the glucose tolerance curve is especially impressive and suggestive.

—Author's Abst.

The chemical and histo-pathological changes in the thyroid in different diseases incident to men (Ueber die chemischen und patholo-

gisch-histologischen Veränderung der Schilddrüse bei den verschiedenen Erkrankungen des Menschen). Nosaka (T.), Folia Endocrinol. Jap. (Kyoto), 1926, Bd. II, s. 2.

Determinations carried out by the Bauman-Anton method showed equal distribution of iodine in different parts of the gland with a gradual increase with age from the embryo to middle life, except for a sudden rise at puberty. After middle age there is a gradual decrease, and generally an atrophy of the gland after the sixtieth year. The weight of the thyroid in the Japanese is much less than in Europeans, but with the iodine content exactly the reverse is true. In pulmonary tuberculosis, tetanus, suppurative inflammation, and uremia there is an increase in iodine and gland weight. In Basedow's and Addison's diseases, acute infections such as enteric fever and miliary tuberculosis, beri-beri and gastric ulcer, there is an increase in gland weight or iodine content, or both. Diabetes, status lymphaticus, icterus and cancer cachexia (except in breast or neck locus) have no definite relation to weight of the thyroid or the iodine content.—E. P. Durrant.

Goitre incidence in New Jersey school children. Reichle (H. S.), Arch. Ped. (N. Y.), 1926, **43**, 329-334.

In the city of Irvington, 2150 children between the ages of 6 to 17 years were examined. Enlarged thyroids were found in 14.7 per cent of the girls and in 3.5 per cent of the boys. There was a marked rise at 9 to 11 years of age, with a drop following this period, and a subsequent rise at the ages of 16 to 17 years. It is logical to assume that the increase between 9 and 11 years is due to influence of adolescence. More factors than iodine content are involved. The thyroid enlargements are purely relative and depend not only on actual hypertrophy of the gland but also on the size and contour of the individual neck. It is obvious that the mensuration of thyroid is quite faulty. It does not seem probable that iodine medication in schools before or during adolescence could reduce the percentage of these physiological goitre of non-goitre districts. No reduction in the size of adolescent goitres was noted even after treatment with iodine for months.—M. B. Gordon.

Lowered metabolic rates, with special reference to young women. Smith (P. S.), South. M. J. (Birmingham), 1926, **19**, 718-723.

In a series of 610 metabolic tests the author finds approximately 45% of the patients with elevated rates and 11% having reduced rates. A plea is made for the promotion of more satisfactory standardization of the various types of metabolism apparatus

and more uniform agreement as to what constitutes an abnormal reading. Excluding the patients with myxedema, cretinism and lowered rates following subtotal thyroidectomy, 31 cases of lowered metabolic rates are reported. Three were males. Ten of the 28 females were of menopausal age and obesity was present in only 25% of the female patients. Special interest is manifested in the incidence of lowered metabolic rates in girls and young women. Of the 31 cases 12 (39%) between the ages of 14 and 25 years are included in the table published. Obesity is usually regarded as a symptom of hypothyroidism, but in these younger patients it was present in only one; five were of normal weight, whereas six (50%) of the twelve patients were definitely underweight. Nervousness, weakness or fatigue—symptoms generally associated with hyperthyroid states—appears seven times (63.5%) as an outstanding complaint in these young females. The records of eight of the twelve patients contain some reference to the thyroid gland; in seven (87.5%) some degree of thyroid fullness was observed. The author concludes that the clinical syndrome of nervousness, unexplained fatigue and thyroid enlargement occurring in young females, many of whom are underweight, cannot be differentiated accurately from hyperthyroidism without an estimation of the patient's metabolic rate. In many such cases with lowered rates thyroid extract appears to have a specific effect.—Author's abstract.

Angina pectoris as a complication in myxedema and exophthalmic goiter. Sturgis (C. C.), Boston M. & S. J., 1926, **195**, 351-354.

A discussion of four cases.—J. C. D.

The antagonism of thymus and thyroid. (Zur Frage des antagonischen Verhaltens von Thymus und Thyreoidea.) Takao (Tokuriu), Arch. f. d. ges. Physiol. (Berl.), 1926, **23**, 192-197.

The loss of liver glycogen in the rat fed thyroid is confirmed. Thymus feeding, either alone, or in different proportions with thyroid, produces no effect. Sodium iodide, in the amounts used, produces no effect. While thyroid feeding produces a marked loss of body-weight, thymus feeding produces a slight rise.—A. T. C.

The thyreotoxicosis syndrome and the reaction with small iodine doses. Wahlberg (J.), Acta Med. Scand. (Stockholm), 1926, Suppl. XIV, 148; Abst. Chem. Absts. **20**, 3505.

The thyreotoxicosis syndrome is characterized by the common occurrence of a disturbance in thyroid function as is evinced not only from a general clinical investigation but also from a study of the basal metabolism, of the alimentary glucemic reaction and of

the blood pressure. In 20 such patients experiments were carried out to determine the effect of small doses of iodine on the clinical condition as well as on the basal metabolism, pulse rate and body weight, the results showing that these patients betray a characteristic sensitiveness toward the iodine. The primary effect is a general improvement which occurs the more quickly and is the more pronounced, the more intense the thyreotoxicosis syndrome, and which involves the entire syndrome (lowering of the basal metabolism up to 60%, reduction of pulse rate by upward of 40 beats per minute, recession of the exophthalmus, cessation of diarrhea, etc.). By continued treatment this primary effect of the iodine is followed by a secondary exacerbation of the syndrome which is quicker in its onset and more pronounced the more serious the patient's condition was. The condition of a patient may, therefore, actually become much worse under the iodine treatment. At the discontinuance of the treatment the condition also becomes much worse, this being the more pronounced the more serious the thyreotoxicosis of the patient was at the beginning of the treatment. The iodine therapeusis must, therefore, be regarded as offering merely a palliative relief, unless it is resorted to as a preoperative and postoperative treatment, and as a method of therapy should be carefully avoided, especially in the more advanced stages of the disease.